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1960

1959 ERNST BISCHOFF LECTURE:
Adventures in Clinical Chemistry

O. H. GAEBLER

During my career in biochemistry and clinical chemistry, three areas of activity have been sources of great satisfaction. First among these is our usual function of developing and supervising chemical laboratories that aid the medical profession in diagnosis, prognosis, and treatment of disease. During 3 years with Prof. V. C. Myers, at the State University of Iowa, and 19 years with Dr. F. W. Hartman, at Henry Ford Hospital, this was my principal assignment. Research was a secondary, but by no means impossible or neglected, pursuit; in fact, many research interests that continue to intrigue me developed during those years. Much of the work in clinical laboratories can be classified as development, for it involves adapting known principles and procedures to practical use; but it also brings one into contact with many challenging problems.

Even prosaic analytical duties may become exciting. One day at Iowa City, everyone had diabetes. All blood sugar reports were held up while telephones jangled and fermentation began at the clinical end of the line. Without my knowledge, but with the best of intentions, the division of analytical chemistry had made our laboratory a present of expensive and highly extracted filter paper, which students in "quant" refused to buy at 2 cents a sheet, because some sheets broke when folded. It was well known at the time that some of the cheapest grades of filter paper contained only traces of reducing substances and prohibitive amounts of phosphate, while some expensive grades were free of phosphate and full of reducing substances.

Although not our principal function, identication of poisons, drugs, and ordinary compounds available at the grocery or hardware store is often expected. While this can be a waste of time or a frustrating venture, I can recall many instances in which it disposed of unnecessary anxiety, exposed fraud, or even established the cause of death. Knowing something about the circumstances may be either helpful or misleading. An alkaline salt from a sack in the garage is obviously available in sackfuls; our sample was sodium carbonate, and nothing to cause alarm. But the white powder which the life of the party took at 3 a.m. was not sodium bicarbonate, as he supposed. It was lead arsenate, apparently selected with indifference from the available packages. Most of the arsenic appeared in the urine, most of the lead in the feces, and results of the mistake were not too serious. Another preparation, thought to be apomorphine, turned out to be tartar emetic, the toxic effects of which are cumulative; it should not have been put into a husband's coffee repeatedly to cure him of alcoholism. A brand new distemper remedy, supposedly imported from Europe, was pure lactose. Panaceas for human ills can usually be disposed of without analysis. If analysis is demanded, it is a good rule to look for ingredients that are more or less harmless and inexpensive.

From the Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit, Mich.
Presented as the Eighth Ernest Bischoff Award Lecture in Clinical Chemistry at the Annual Meeting of the American Association of Clinical Chemists, Aug. 27, 1959, Cleveland, Ohio.

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A second field in which I have been privileged to participate is teaching. In this connection, it might be wise to consider a situation that we may face in the near future. In some highly respected departments of biochemistry, candidates for the Ph.D. degree are no longer required to learn blood and urine analysis. Why should they clutter up their minds with "old stuff" when there is such a wealth of recent knowledge they must have if they are to survive as biochemists? Medical students, on the other hand, are taught blood and urine analysis and are introduced to a great deal of new material. So the M.D. of the near future will have background information to set him thinking, and should be ready to consider recent as well as long-established developments when he gets to the clinic. This is as it should be.

Should the prospective Ph.D.'s in biochemistry be denied contact with our field that might be beneficial to it and to them? Should they be warned against clinical chemistry as a purely routine pursuit in an area where chemists or biochemists who enter will be devoured by dragons? Such attitudes are not realistic. Not long ago, the head of a well-known university department of biochemistry said to me: "I could replace any other member of my staff on short notice, but not the clinical chemist." Perhaps clinical chemists who are willing and able to teach, and who know the value and limitations of their field, could be useful in this connection.

The theme that men in fields of applied science should participate in teaching is receiving considerable attention in professional journals. An opportunity to do so came to me in 1934, when the chemistry department of Wayne University (now Wayne State University) asked me to start courses in general biochemistry and biochemical methods of analysis. After devoting evenings to this for many years, I consented to fill an unexpected vacancy in physiological chemistry, with intermediary metabolism as my lecture topic — for the next 7 years. Many treasured associations with faculty and students resulted, particularly with the eight candidates for the M.S. degree and 5 for the Ph.D. degree, who completed their research requirements under my supervision.

My third topic is research. During one of his frequent visits to our hospital, the late Charles F. Kettering commented that he and his associates did a lot of research that was published in the form of better automobiles. Many of us must do a great deal of investigation of this type, but if one examines more formal publications it can be seen that quite a few are in three very interesting areas: isolation and identification of compounds, methods of analysis, and metabolic problems. Studies I have selected for discussion are in these areas.

A stimulating and provocative study by Behre and Benedict[1], which appeared in 1922, presented strong evidence for the absence of creatinine from normal blood. From the Folin picric acid blood filtrate, kaolin did not remove the apparent creatinine, while creatinine added to blood was transmitted to this filtrate and removed by kaolin. My first paper on the topic of isolating creatinine[2] begins with an erroneous statement: "The use of kaolin in removing creatinine from dilute solutions is disadvantageous in that the absorbed creatinine can not be released again for identification." Benedict later told me that creatinine can be released from kaolin with

magnesium oxide suspension, and that this treatment also releases a chromogenic substance from kaolin with which a Folin picric acid filtrate of normal blood has been shaken. Kaolin was, however, a bulky adsorbent.

In my first isolation procedures, creatinine was concentrated from blood filtrates by adsorbing it on the potassium salt of a new complex acid[2,3] which we called picrophosphotungstic acid, or on Lloyd's reagent[3,4]. The base was then isolated as creatinine potassium picrate. This was converted almost quantitatively to creatinine zinc chloride, which was analyzed for nitrogen content per milligram of creatinine. Thus identification rested upon preparation and partial analysis of two derivatives. Linneweh[5] modified one of our procedures, obtained the gold salt of creatinine from beef blood, and submitted it to elementary analysis.

In subsequent studies[6,7] we used serum. Initial dilution was avoided by ultrafiltration, since precipitation technic had meanwhile been improved so that creatinine could be precipitated directly from ultrafiltrate. Progress in precipitating creatinine was the result of the activities of a series of investigators (Table 1). The solubility of creatinine potassium picrate in water, which Jaffe[8] recorded, calculates to 33.4 mg. of creatinine per 100 ml. Morris[9] reduced this to 5.0 by saturating the supernatant with picric acid. By adding an excess of potassium, Gaebler and Keltch[3] reduced it to 3.0, or even to 0.6, in initial precipitations in which contamination with potassium picrate did not matter. Greenwald and Gross[10] studied the solubilities of double picrates of creatinine with potassium, rubidium, and cesium, and found the one with rubidium to be least soluble. By utilizing this information, and carrying out precipitations in the refrigerator, we found that known creatinine could be precipitated so completely that less than 0.1 mg. per 100 ml. remained in the supernatant[4].

With this technic, creatinine was readily precipitated from ultrafiltrates of normal human, dog, beef, and pig sera[6]. In isolation experiments on animal sera, we used an ultrafilter that produced 200 ml. of ultrafiltrate from 300 ml. of serum in 2 hours. Creatinine from beef serum and pig serum was readily accumulated and identified[7]. Creatinine from beef blood[3], dog blood[4], blood and transudate of human nephritics[3], and dog blood obtained during experimental retention of various types[3,4] had been identified previously.

While these results were very tangible and gratifying, they did not completely satisfy my curiosity. Our first isolation procedures[2], when applied to normal blood, were inefficient enough to avoid serious conflict with evidence for absence of creatinine from normal blood.[1] As our isolation methods improved,[4] our troubles increased, and when we began to wonder about the validity of the kaolin experiment, it turned out that our precipitation method, under suitable conditions[6,11], could also be used to precipitate added creatinine without precipitating the creatinine of normal blood. To this day, I have the feeling that the story of creatinine in normal blood is not fully known.

It is, indeed, interesting that induced enzyme formation appeared on our horizon during the resolution of this problem. Miller and Dubos[12] used a creatinine-destroying enzyme, formed by soil bacteria grown on a medium in which creatinine

Table 1

Conditions Affecting the completeness of Precipitation of Creatinine as a Double Picrate.

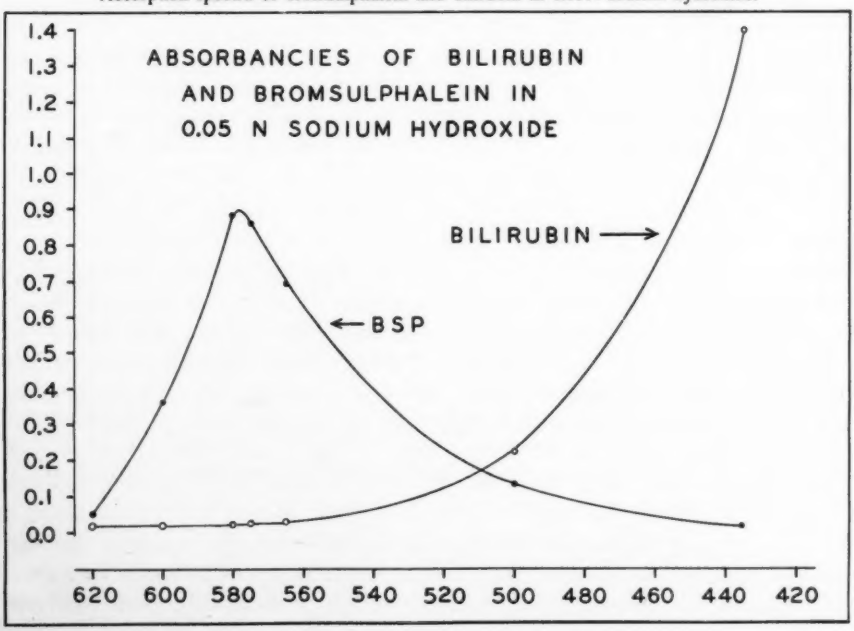
		Solubility of creatinine (mg./100 ml.)
Creatinine potassium picrate		
In water (Jaffe, 8)		33.4
In saturated picric acid (Morris, 9)		5.0
In saturated picric acid, with potassium ion in excess	1.21:1	3.0
(Gaebler & Keltch, 3)	1.36:1	1.9
	1.51:1	1.4
	3.0 :1	0.6
Rubidium creatinine picrate, (Greenwald and Gross, 10)		
In saturated picric acid, with Rb ion in excess temp. 5.0°C.		
(Gaebler, 6)		<0.1

supplied the nitrogen, as a means of securing evidence for presence of creatinine in blood. However, creatine was thought to be present as such in muscle from 1835 until 1929, when Fiske and SubbaRow[13] described their isolation studies on creatine phosphate, existence of which could have been missed by a variety of "specific" methods.

Of several ventures into the field of analytical methods, determination of bromsulphalein[14] best illustrates the difference that appearance of photoelectric colorimeters and spectrophotometers has made in our work, and the problem that differences in design of the various instruments created.

Figure 1

Absorption spectra of bromsulphalein and bilirubin in 0.05N sodium hydroxide.



Bromsulphalein (BSP) was formerly determined with a test tube comparator[17] obtainable from the sellers of the indicator. That the color of alkaline BSP in icteric sera could not be matched with the BSP standards was mentioned in several papers. When examined in a Beckman spectrophotometer, the absorption spectra of alkaline solutions of bilirubin and BSP are about as different as possible (Figure 1). Although the eye is an amazing optical instrument and detects differences in wave length as well as intensity, its "band pass" is arranged for outdoor purposes. Differences in the band pass of various instruments also create a problem.

In one of our two procedures[14], we applied two-color spectrophotometry, which enabled us to use a water blank, and reduced the amount of serum required to 0.5 ml. BSP concentration (X) was calculated from the absorbancies (A_s) of the solution at 580 mμ and 620 mμ as follows:

$$X = \frac{A_s^{580} - K_1 A_s^{620}}{0.0715\left\{1 - \frac{K_1}{K_2}\right\}} = \frac{A_s^{580} - 1.2\,A_s^{620}}{0.0715\left\{1 - \frac{1.2}{14.3}\right\}} = \frac{A_s^{580} - 1.2\,A_s^{620}}{0.0655}$$

The absorbancy of BSP, per milligram, at 580 mμ, with dilution, cell depth, and other conditions as specified, was 0.0715. In the spectral region between 620 and 580 mμ effects of light scattering by normal or slightly turbid serum, and absorption by hemoglobin or bilirubin, were small and similar. K_1 was the ratio of absorbancy at 580 to absorbancy at 620 mμ, deriving from this composite source; K_2, the absorbancy ratio for BSP at same wave lengths.

Difficulties with this procedure arose when the Coleman Junior Spectrophotometer, with a band pass of about 35 mμ, was used. K_2 was 14.3 when absorbancies were determined with the Beckman instrument, which has a very narrow nominal band width, and 3.7 when the Coleman Junior was employed. Small differences in the average value of 1.2 for K_1 were unimportant when K_2 was large, but significant when K_2 was small. It was necessary to choose different wave lengths for the Coleman Junior, or to use the alternative method of calibration given in our paper (Eq. 2, Ref. 14). Newer procedures for determination of BSP have appeared[18,19] and reference to my procedure has been made to illustrate certain principles.

Since turbidity correction entered into two of our methods[14,15], I may say that the linear relationship between log of the absorbancy due to turbidity, and the negative logarithm of wave length[16] has been confirmed with a number of Beckman instruments. It does not apply for wave lengths in the near infrared, or when instruments with wide band pass are used. The best correction for all interferences that can be avoided is to avoid them. If turbidity can not be avoided, one has a choice between correcting for it by a method such as that which we used, or of decolorizing the substance to be measured and subtracting the resulting blank[19,20].

My interest in metabolic studies began while I was a candidate for the Ph.D. degree at Toronto, and has been a continuing one. In their pioneer work on gigantism in rats, Evans and Long[21] used alkaline extracts of beef anterior pituitary. Putnam, Benedict, and Teel[22] used it in simulating acromegaly in dogs. Teel salted out the globulin fraction, which contained several anterior-lobe hormones. Such preparations

were made available to me by members of the research staff of Parke, Davis & Company. My first experiments[23,24], carried out in 1932, were so striking (Fig. 2) that I soon developed a long-term interest in metabolic effects of anterior-pituitary hormones. When a dog receiving a constant amount of food increased its weight by 1½ lb. within 48 hours and stored quantities of nitrogen, in spite of an increase of more than 40 per cent in basal metabolic rate, it seemed to be high time to investigate! It was well known that a similar increase in metabolic rate induced by intravenous thyroxin is accompanied by marked losses of weight and nitrogen. There was, as usual, nothing thermodynamically illegal about the behavior of our dog. The fall in nonprotein respiratory quotient was due to greatly increased oxidation of fat, not failure to oxidize carbohydrate. Available carbohydrate apparently ran low during the post-absorptive period, since all of the extra calories could be supplied by carbohydrate if a sufficient amount was added to the diet when the anterior pituitary preparation was given[24].

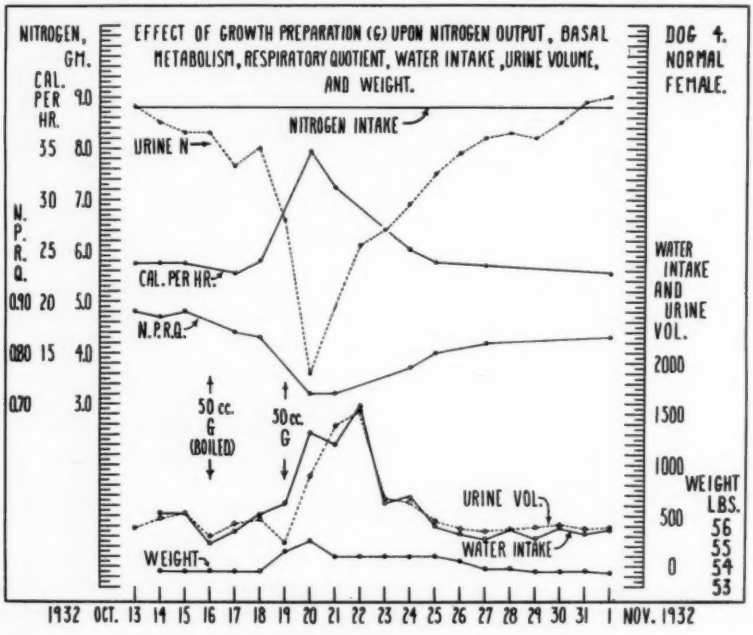

EFFECT OF GROWTH PREPARATION (G) UPON NITROGEN OUTPUT, BASAL METABOLISM, RESPIRATORY QUOTIENT, WATER INTAKE, URINE VOLUME, AND WEIGHT.
DOG 4. NORMAL FEMALE.
NITROGEN, GM.
CAL. PER HR.
N. P. R. Q.
NITROGEN INTAKE
URINE N
CAL. PER HR.
N.P.R.Q.
50 cc. G (BOILED)
50 cc. G
WATER INTAKE AND URINE VOL.
URINE VOL.
WATER INTAKE
WEIGHT
WEIGHT LBS.
1932 OCT. 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 1 NOV. 1932

Figure 2

Changes in nitrogen output, basal metabolic rate, nonprotein respiratory quotient, water intake, urine volume, and weight in a normal bitch treated with crude growth hormone (*G*).

Nor was storage of nitrogen spurious. The nonprotein nitrogen of the blood, as previously reported by Teel and Watkins[25], fell during such experiments, and we found no change in fecal nitrogen. So began a long-term program with which we are still occupied. Effects of growth hormone and corticotropin on nitrogen metabolism, and the relationship of insulin to the latter effect, have been principal foci of our interest. Highly purified growth hormone, assayed for residual impurities, has been made available to us by the Endocrine Study Section, National Institutes of Health. With this

preparation, we have verified our early finding[26] that in depancreatized dogs receiving a constant amount of food and insulin, nitrogen storage is not induced by growth hormone but is induced if the insulin dose is increased when growth hormone is given[27]. We also found the purified growth hormone, which is virtually free of corticotropin, as diabetogenic as earlier crude preparations in the depancreatized dog. Since diabetogenic effects of crude preparations were mild in adrenalectomized depancreatized dogs[26], there is further work ahead.

Morphologic and physiologic effects that endocrine glands exert upon one another, as well as synergisms between products of these glands, create a rather complicated situation. Nowhere is this better illustrated than in the stubborn problem of calorigenesis, recently attacked with renewed vigor by Evans, Contopoulos, and Simpson,[28] and Evans, Simpson, and Evans.[29] Transferring from the multiorgan level to the subcellular ribonucleoprotein particle, one finds interesting studies on protein synthesis and on effects of growth hormone by Balis *et al.*[30]. The pituitary will continue to provide problems for many scientists for some time.

At our last previous scientific meeting, in Washington, D.C., I presented some studies[31] on effects of growth hormone and corticotropin on metabolism of N^{15} from glycine, alanine, and ammonium citrate. I will close with another study[32] that has not been discussed with this group. Studies of Bartlett and Glynn[33,34], Beaton *et al.*[35], and Zuchlewski and Gaebler[36] indicated that growth hormone alters the activity of glutamic oxalacetic transaminase in muscle, and particularly the glutamic pyruvic transaminase in liver (see Fig. 4, Ref. 37). The profound reduction in activity of hepatic GPT naturally aroused our interest in knowing whether the nitrogen transfer pattern is altered.

In recent studies by Lees and Gaebler[32], each of four groups of hypophysectomized rats received, by intraperitoneal injection, one of the four N^{15}-labeled amino acids—glycine, L-alanine, L-aspartic acid, and L-glutamic acid. The groups were divided into untreated control and growth-hormone-treated subgroups. Forty-eight hours after injection of the labeled amino acids, the animals were sacrificed. Proteins from the myofibrillar fraction of muscle were hydrolyzed, and 7 amino acids, as well as ammonia, were isolated by column chromatography. Mass spectrometer determinations of N^{15} excess in these compounds yielded several results of interest. The amino acids from control groups, with the exception of threonine, were labeled. Alanine, glutamic acid, and aspartic acid, as well as amide nitrogen received considerable amounts of N^{15}. When N^{15}-glycine was given, serine was heavily labeled. These findings are well known in the case of normal rats; the point of interest is that nitrogen transfer was not essentially altered in the absence of pituitary hormones. Growth hormone greatly increased the extent of incorporation of N^{15} into the amino acids and amide nitrogen of myofibrillar protein, but did not alter the nitrogen transfer pattern.

While browsing in a book containing aphorisms of Sir William Osler[38], I came upon the following: "One can get along with a few ounces of kidney and less liver. The liver is comparatively harmless and useless. It was put in merely for packing purposes." No doubt, the last two quoted sentences were only meant to emphasize the first one. I do not mean to imply that determination of tissue enzyme activities is

a useless pursuit, on which my associates and many other investigators have wasted a lot of time, but I do feel that if one can get along with so little liver or kidney, the significance of even large changes in tissue enzyme activities must be considered with caution. Whenever an experimental approach is possible, experiments with the substrates in question should be carried out.

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THE BIOCHEMICAL AND STRUCTURAL ORGANIZATION OF MITOCHONDRIA

The Ninth Edsel B. Ford Lecture†

ALBERT L. LEHNINGER, Ph.D.*

Recent research on the mechanism of oxidative phosphorylation, the swelling and contraction of mitochondria, and their ultrastructure, has made possible some new correlations between the action of the respiratory enzymes, the structural states of these cellular "power plants", and new information on control mechanisms.

It is now established that the double membranes of the mitochondrion contain catalytic "assemblies" of molecules of the phosphorylating respiratory chain enzymes which exist in recurring units, a single liver mitochondrion having perhaps 10,000 of such "assemblies", which thus make up a substantial fraction, perhaps up to 40%, of the lipoprotein substance of the membranes. These membranes are not simply "dead" walls, but actually complex multienzyme systems which could be expected to confer some specificity and control over the exit and entry of substrates and end products and thus control the metabolic functions of the mitochondria.

The isolation and identification of the specific enzyme molecules participating in the respiratory chain and in the energy-coupling mechanisms thus not only reveal information about the mechanism of oxidative phosphorylation, itself one of the most fundamental problems in contemporary biochemistry, but also provide information about the molecular structure of the membrane. Two intermediate enzymes of energy coupling have been obtained in soluble, highly purified form from fragments of the mitochondrial membrane. The first is an enzyme catalyzing the reversible exchange of labeled ADP with unlabled ATP, which is responsible for the terminal step in ATP formation. This soluble purified ATP-ADP exchange enzyme can be recombined again, with specific, empty binding sites on the membrane fragments, to restore the normal enzymatic connection of this enzyme with a preceding enzyme of the energy-coupling sequence. This specific recombination of the nucleotide exchange enzyme requires a second soluble purified protein, designated M-factor, which may be the preceding enzyme of the coupling sequence. Availability of these two proteins in purified soluble form thus makes possible partial reconstruction of this "solid-state" enzyme system and with it, partial reconstruction of the functional membrane.

These developments have been paralleled and supplemented by studies of the biochemical aspects of the specific swelling and contraction of intact mitochondria, both of which are processes dependent on the function of the respiratory assemblies in the mitochondria membrane. The "active" swelling of mitochondria, with uptake of water, as induced by the specific intracellular agents Ca^{++}, phosphate, thyroxine, or reduced glutathione, requires electron transport along the respiratory chain, since it is inhibited by the respiratory chain inhibitors, cyanide and antimycin A, as well as by the uncoupling agent 2,4-dinitrophenol. Swelling of mitochondria is also prevented

*DeLamar Professor of Physiological Chemistry and Director The Johns Hopkins University School of Medicine, Baltimore, Maryland.

†Presented on October 11, 1960, at Henry Ford Hospital, Detroit.

by the presence of ATP. The action of specific swelling agents is also prevented when the mitochondria are made anaerobic and it is now certain from such experiments that some respiration is necessary in order for the mitochondria to be susceptible to the action of these specific swelling agents.

When mitochondria swell in the presence of these specific agents, they not only take up water, but they increase their permeability to certain test solutes such as sucrose. They also undergo enzymatic changes. The first change which is evident is a loosening of the normally "tight coupling" between phosphorylation and respiration i.e. respiration loses its dependence on the presence of ADP. The "loose coupling" of respiration produced during swelling signifies the loss of an important control over the rate of respiration; for example this condition is often seen in mitochondria isolated from hyperthyroid rats. On further swelling, other changes occur. DPN is lost from the mitochondria on drastic swelling and the ability to phosphorylate ADP then diminishes. "Active" swelling thus causes changes not only in the morphology and volume of the mitochondrion but also in the integration and control of the complex respiratory chain and its energy-transducing mechanisms.

Mitochondria which have undergone swelling by such agents can be contracted again by the addition of ATP. The contraction of mitochondria, like the swelling phase, is also geared to the action of the respiratory chain and the coupling enzymes; however the mode of "gearing" is different in the two phases. Anaerobiosis and inhibition of the respiratory chain do not prevent contraction by ATP, nor does dinitrophenol. On the other hand other uncoupling agents for oxidative phosphorylation such as sucrose and sodium azide do prevent the contraction, which therefore requires the integrity of only a portion of the repiratory assembly, particularly the enzymes responsible for the formation of ATP.

During contraction of mitochondria induced by ATP, water is extruded; as many as 3000 moles of water may be extruded per mole of ATP split. Since the contraction and water extrusion proceed at a rate which is relatively independent of the ionic composition of the medium and occurs also in mitochondria which no longer are capable of active transport of K^+, it is concluded that the water extrusion is the result of a contractile process in the membrane, rather than a secondary process to active ion transport.

These findings thus indicate that mitochondrial structure and volume represent a dynamic balance between forces tending to cause swelling and those tending to cause contraction of the structure. Such a picture could account for the plasticity of shape of mitochondria seen in certain types of cell such as the fibroblast. It appears possible that the swelling and contraction cycle is involved in active transport and water movement in cells, such as the renal tubule cell, where it is now known from the work of Rhodin that the mitochondria are aligned in the axis of active transport. Such changes of structure which are geared to reaction of the respiratory chain, are also in turn capable of causing alterations in respiratory rate or in respiratory control by either phosphate or ADP, thus suggesting the occurence of a complex feed-back control system.

To account for the change in membrane properties in the presence of ATP, it is postulated that some of the enzyme molecules present in the mitochondrial membrane are "mechano-enzymes", a term that Engelhardt originally proposed to designate contractile proteins such as actomyosin. Thus if the coupling enzymes in the respiratory chain are capable of a change of shape, configuration, or charge distribution, depending upon whether or not they are in the phosphorylated state, then it is possible to see how the mechanical properties as well as the permeability changes are a function of the respiratory state of the membrane. Actually actomyosin, the contractile element of muscle, and the energy coupling systems of the respiratory chain have many biochemical features in common such as their ATP-ase activity, nucleotide specificity, stimulation by dinitrophenol, and the occurrence of O^{18} exchange reactions, all of which suggest a functional similarity between the two types of system.

The relationship of the swelling and contraction cycle to the mechanism of oxidative phosphorylation has been emphasized by our recent finding that a specific mitochondrial protein called C-factor is required to effect contraction of swollen mitochondria in the presence of ATP. This protein has been extracted from mitochondria and obtained in purified soluble form. It has now been found that such C-factor preparations are also rich in M-factor activity. It will be recalled that M-factor is the protein which is necessary to cause the enzymatic connection between the ADP exchange enzyme and the respiratory chain enzymes in the energy converting mechanisms. While further purification is necessary to prove identity beyond a doubt, if they are identical, then it is evident that an intermediate protein of the energy coupling mechanism is also involved in the contraction of mitochondria, thus giving direct support to the "mechano-enzyme" hypothesis.

These investigations thus show the enzymatic complexity of the mitochondria and reveal possible approaches to study of the ultimate molecular biology of membraned systems.

More complete accounts of this and related work, with full literature citations, are given in the following articles:

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CROSSED-PIN TECHNIQUE IN MANAGEMENT OF COMPLEX TIBIAL FRACTURES

HAROLD M. FROST, M.D.*

INTRODUCTION

This paper considers a method of treatment of complex tibial fractures which requires little armamentarium. The method's chief usefulness lies in the management of tibial fractures accompanied by severe instability and severe soft tissue injury. The technique is called the crossed-pin technique.

The crossed-pin technique is not original with the writer. It has not been described in the literature, although techniques which resemble it are on record. The writer acquried the technique from J. D. Godfrey, M.D. of Buffalo, New York. While reference to a similar technique attributed years ago to Dr. Steindler of Iowa City appeared in a state medical journal, the reference could not be found in that journal or its neighboring issues. In any event, the technique is not original, has not been published but is in use by occasional surgeons throughout the country. The Stader and Roger-Anderson techniques are developments of the basic crossed-pin idea. In the past, all three of these techniques (the crossed-pin, Stader, and Roger-Anderson) have suffered unjustly and badly in reputation due to misuse, usually consisting of short-cuts which circumvented certain necessities inherent in the use of the techniques. For this reason the writer wishes at this point to fix firmly in the reader's mind that *the techniques described, while inherently simple, is accompanied by considerable risk if the "Don'ts", which are an essential part of the technique, are disregarded. There is no leeway in these "Don'ts".*

The writer's personal experience with this technique will be summarized later. It includes 43 injured legs which contained over 120 fractures. Three-fourths of the legs contained compound fractures and one-fourth contained additional serious loss of bone and soft tissue.

Crossed-pin technique

This technique will be presented as a series of steps.

1. The first step is the proper treatment of all open wounds and damaged soft tissues. Since the indications and methods for this phase of the management are standard surgical procedure and not germane to the main thesis they will not be elaborated.

2. The basic idea of the crossed-pin technique is to drill two Steinman pins in the proximal fragment and two in the distal fragment of the tibia, the pins in each fragment being oriented at 90 degrees to each other and all pins being drilled through the near cortex but *not* drilled completely through the far cortex. They are simply toed into the far cortex for suitable anchorage. They are usually drilled proximal and distal to the fracture hematoma, not through the fracture hematoma. The pins used must be ⅛ inch in diameter or larger and should have the drill point rather than the stylet point on them. (Fig. 1).

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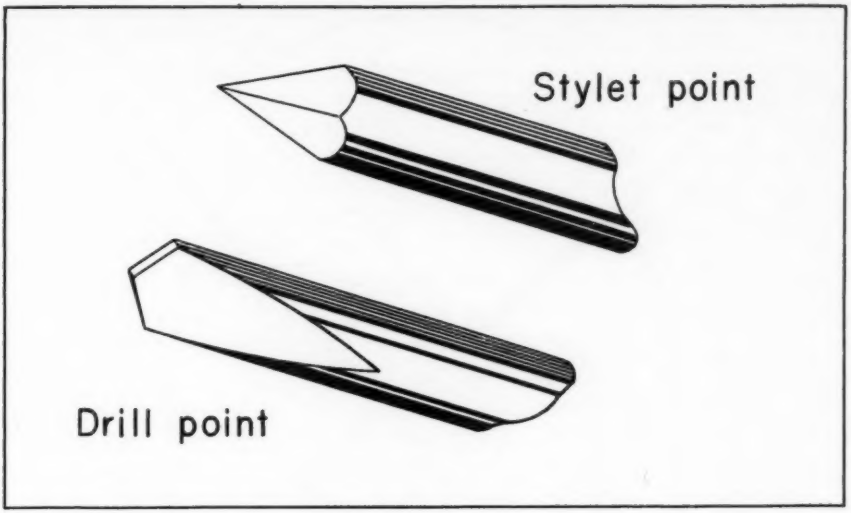


Figure 1

The stylet pointed pins should not be used to drill through thick, cortical bone. The point acts as a wedge and tends to split the bone. Terrific frictional heat is produced when drilling this point through cortex. The heat literally cooks the surrounding bone and sift tissue.

The drill point cuts its way through cortex and is therefore the more satisfactory of the two points.

The pins are drilled through bone through a small ¼ inch stab wound after suitable local skin preparation. The usual arrangement of the pins is demonstrated in the illustrations. (Figs. 2, 3).

3. After the pins are in place, sterile dressings are impaled upon them and worked down to the skin to keep the unsterile cast padding away from the wounds. If the cast is to be applied while simultaneous os calcis traction is being applied, insertion of the Kirschner wire in the os calcis is done at this time. Os calcis traction has not been necessary in most of the writer's cases because of the unique suitability of the crossed-pin technique for precision wedging.

4. The cast padding is then applied and *must* be for a long leg cast with the knee in 30 or more degrees of flexion with the cast extending to the groin. Since this cast is worn for ten to twelve weeks, the first layer may be stockinette which will avoid wadding up of the padding over time. About this time (before if stockinette is used) the pins should be cut off, leaving approximately two inches protruding out of the skin.

5. A loosely compacted wad of padding approximately ¾" in thickness should be fashioned in such manner that it completely pads the anterior surface of

(a)—The stylet point requires too much orce to drill through cortical bone, produces too much frictional heat which bakes surrounding tissue and in addition may split a fragment, producing an additional fracture, due to its wedge eflect.

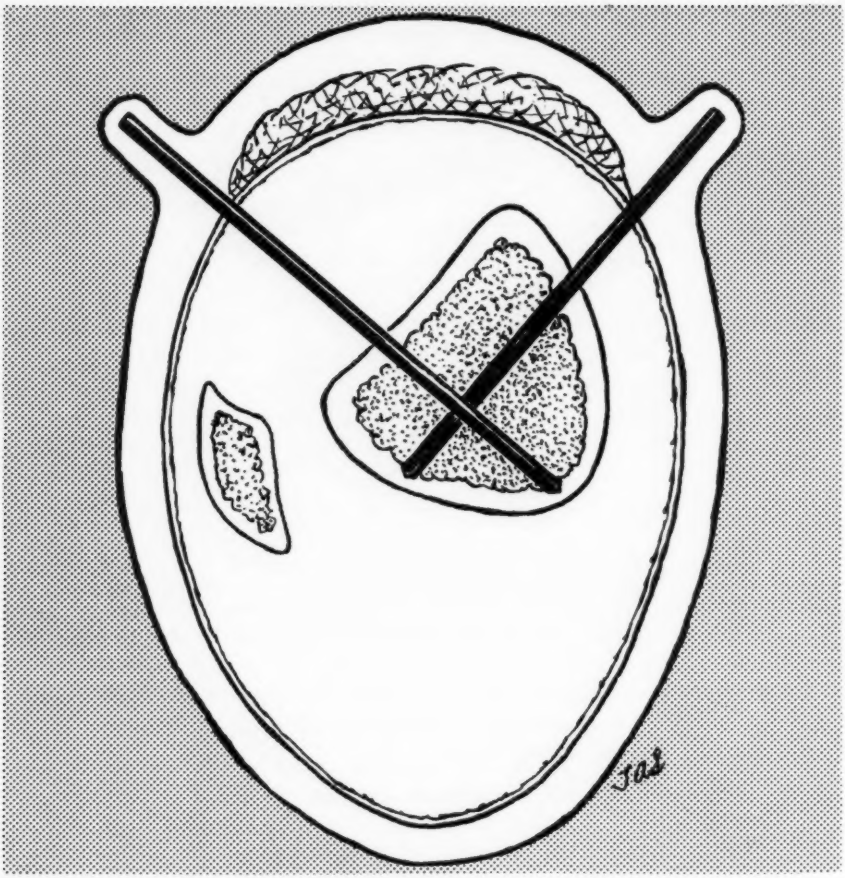


Figure 2

Cross section of leg, diagrammatic, with pins in the tibia. The pins are toed into, but not drilled through, the second cortex. The extra padding between cast and shin — depicted diagrammatically at the top — protects the skin from slough after wedging.

the tibia between the two sets of pins. (Figs. 2, 5). This protects the skin from pressure by the edges of the cast following wedging and *failure to incorporate this extra padding in the cast may lead to a slough.* When in doubt about the safety of the skin after wedging, inspection of the lateral x-ray will reveal the relationship of skin and cast satisfactorily.

6. The leg is now dropped over the edge of the operating table and while an assistant holds the toes, plaster is wrapped on from the tibial tubercle to the toes, incorporating the pins. Additional plaster as needed is wrapped over the tops of the pins so that all metal is covered. The plaster must be well molded around the pins so there is no play between pin and cast. At least an

inch of pin and preferably an inch and a half should be so incorporated in plaster. Placing corks or other such devices on the ends of the pins defeats the underlying purpose, which is to rigidly attach each fracture fragment, via its set of pins, to the cast. The assistant holding the toes should be instructed to let the leg hang of its own weight to avoid posterior bowing of the fragments and should be shown how to control the torsional relationship of the fragments. Any malposition and malalignment may be corrected by wedging but correction of torsion in addition to position, length and alignment complicates wedging considerably.

7. When the below knee part of the cast is solid, the leg is then elevated by means of sling or held by assistants while the above knee portion of the cast is applied and allowed to set.

8. Correction of position, alignment, and rotation may be done immediately, or several days later, by wedging. Wedging first necessitates accurate AP and lateral x-ray views of the fracture in the cast. The level of the fracture (or, if a segmental injury, of the fractures) is identified on the cast by a circumferential pencil mark. On the anterior aspect of the cast the long axes of the

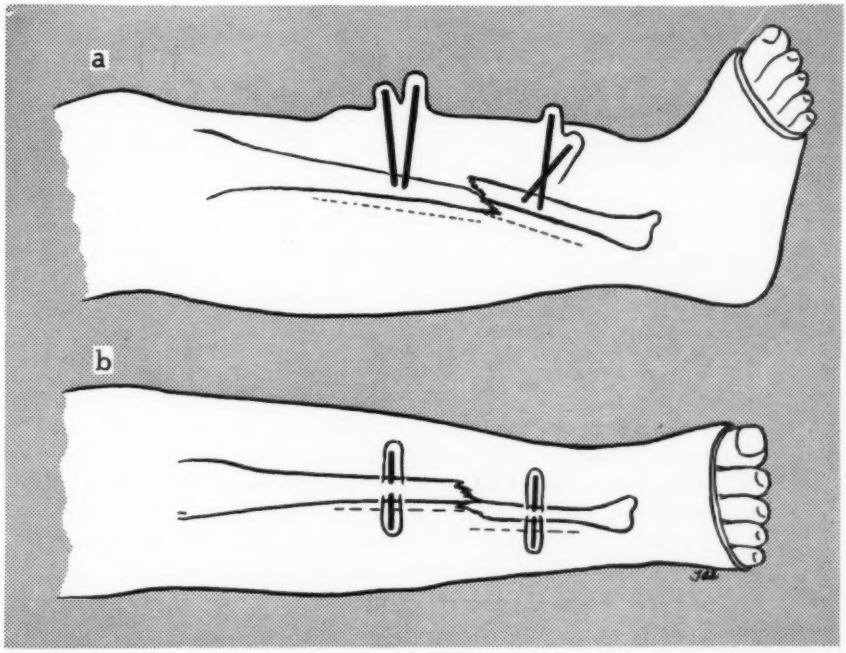


Figure 3

Diagrammatic representation of a specific case. The pins are in, cast is on, pins incorporated and capped by plaster. Long leg cast with 30° knee flexion. Lateral view above, anteroposterior below. The dotted lines represent the lines actually drawn on the outside of the cast from the corresponding x-ray views.

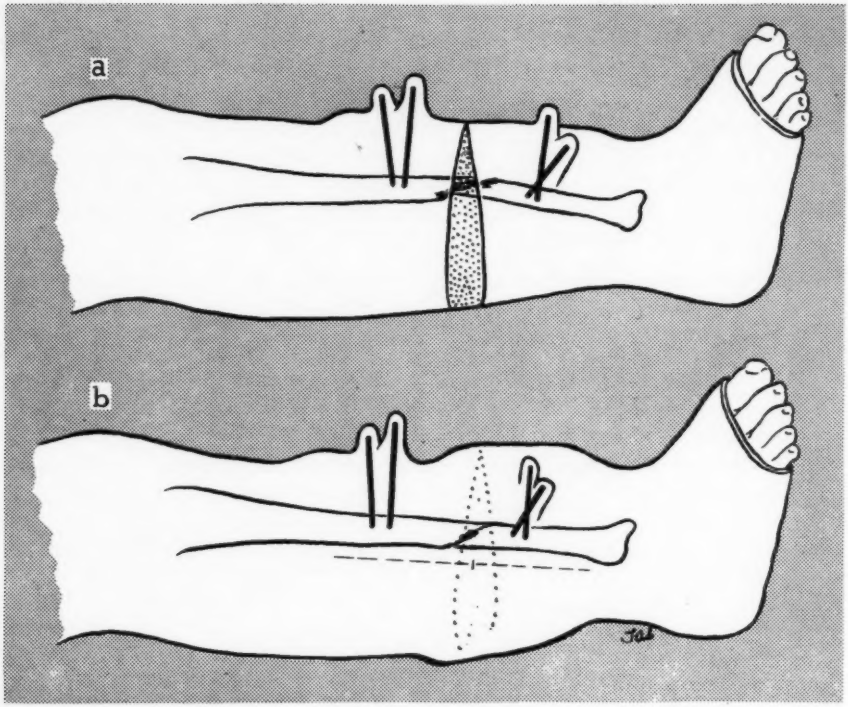


Figure 4

(a) A single, circumferential saw cut at the level of the fracture is made. The shaded area represents the gap that will result when the angulation is corrected. The shaded area does not depict, in this instance, plaster to be removed.

(b) After wedging (correction of angulation and displacement) the fragments are properly positioned and aligned. The wedge is covered by an additional roll of plaster. Wedging is accomplished simply by adjusting the parts of the cast proximal and distal to the wedge cut until the dotted lines are parallel and abut on each other.

bones as visible in the AP x-ray view are drawn, producing at the circumferential pencil mark the amount of angulation and malposition which is measured with ruler and protractor on the x-rays. Then one similarly duplicates, by drawing on the lateral aspect of the cast, the long axes of the fragments with angulation and malposition as revealed on the lateral x-ray view. At the conclusion of these steps, the cast contains drawn on it a replica of the long axes of the bones exactly as they lie within the plaster case.

9. If distraction or overriding are present the amount should be measured on the x-rays. In the case of distraction, an additional circumferential pencil line separated from the original one by the exact amount of distraction is drawn on the cast. If there is overriding, two or three spacers are made from layers of tongue blades, such that the thickness of each spacer equals the amount of overriding.

10. A circumferential saw cut is now made around the cast so that the proximal and distal portions of the cast are now separated at the circumferential pencil mark and free to shift position, angulate, and twist on each other. Length correction is produced first, the method being to resect a circumferential ring of plaster equal in width to the amount of distraction, or to insert prepared spacers in the circumferential cut to add length. The cast fragments are then manipulated by hand until the lines representing the long axes of the bone fragments abut end to end and are parallel. If resistance is encountered in this procedure, which is often, it is because the fragments catch on each other. Their resistance is transmitted via the pins to the surgeon's hands. By combinations of torsion, angulation, and displacement it will be possible to "get over the hump" and secure proper position and alignment. A four inch plaster roll is then wrapped around the wedged level, allowed to set, and check x-rays taken. If satisfactory, which is usually the case, an additional wedging six inch plaster roll is wrapped around and allowed to set. If additional wedging is necessary the first four inch roll is removed and re-manipulation performed. (Figs. 3, 4).

11. At the conclusion of this procedure proper length, alignment, and position of the fragments have been restored and secure knowledge that the fragments are immobile exists because they are firmly fixed to the cast by the pins. There is no risk of subsequent slipping. This cast remains on for ten or twelve weeks. At the end of that time there is enough union so that danger of subsequent displacement, angulation, and torsion is nil. The cast and pins are then removed and replaced by a closely fitting long leg cast for an additional eight weeks, at which time union is usually solid enough to begin partial weight bearing. In removing the initial cast the pins are extracted merely by twisting off the

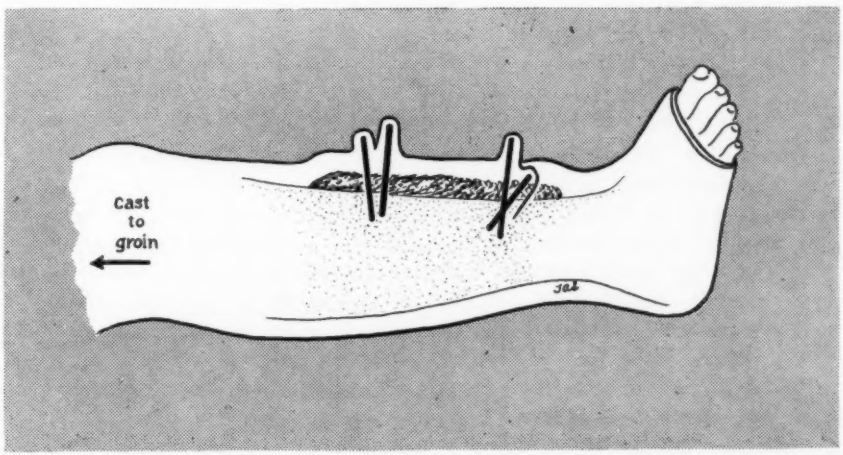


Figure 5

The thick, loose wad of padding between the pins is essential to protect the subcutaneous tibial skin from slough after wedging.

end of the plaster covering them and extracting them with pliers. Since the ends of the pins are buried in tissue and are sterile there is no need to expose the skin in removing them. The pins are usually firmly embedded so a stout pair of pliers is needed for their removal.

CROSS-PIN TECHNIQUE "DON'TS"

A. Don't use pins smaller than ⅛ inch in diameter. They are too flexible and will fail to control the fragments, permitting loss of position and angulation in the cast after wedging.

B. Don't use stylet pointed pins. Use only the drill pointed pins. The heat produced in drilling with stylet points cooks a sizable volume of surrounding tissue which subsequently cultivates myriad bacteria and leads to a very "wet" pin tract.

C. Don't omit the loose padding over the subcutaneous surface of the tibia. If omitted, wedging may produce pressure on the skin and a slough. If inspection of the lateral x-ray after wedging reveals that the skin in the area of wedge is too close to the plaster for comfort, then remove a 4 to 5 inch wide strip of plaster between each set of pins, fill the defect with accurately fitted sheet wadding and cover it over with plaster. This changes the displacement at the wedging line from an abrupt discontinuity to a gradual one.

D. Don't apply corks or other padding to the end of the pins. They must be completely and solidly encased in plaster. Lack of an external plaster cap permits the pins to work out during the subsequent ten weeks so a covering cap of plaster is necessary.

E. Don't drill the pin entirely through the far cortex. When a pin is mistakenly drilled all the way through both cortices, it usually will migrate, usually deeper into the leg, while the outer end of the pin withdraws from its plaster socket, thus leading to loss of fixation. Occasionally these events lead to sepsis or to a subsequent operation to find and remove the pin. Bending the exposed pin end through a 90 degree angle will prevent migration if both cortices are penetrated.

F. Don't ever combine this technique with a short leg cast, or a cast with less than 30 degrees knee flexion, or a cast which does not extend to the groin. The interfaces between pin-and-bone and pin-and-plaster will remain solid for a ten week period only if the loads on these interfaces are below a certain limit. Empirically, the protection provided by the long leg cast is sufficient. Empirically, the lack of proper above knee cast extension leads to loose, then wet, and then infected pin tracts with loss of fixation and often mal-union. Pins are like money; not inherently bad; just good or bad according to the use made of them.

G. Don't be afraid to bivalve a cast with crossed-pins in it. It may be bivalved in such a manner that all four pins (or more if the circumstances of the case required it) remain encased in one or the other half-shell. They continue

to provide fixation. Using this technique and by fashioning plaster outriggers to hold the proximal and distal portions of the cast solidly together, it is possible to combine the crossed-pin technique with subsequent soft tissue treatment, such as skin grafting, in the region without loss of efficient fixation.

DISCUSSION

1. The writer's personal experience encompasses the use of the cross-pin technique in 43 injured legs which contained over 120 fractures in 36 patients, 7 with bilateral leg fractures. In 32 of these legs, one or more of the fractures were open and in 11 of the legs there was moderate to severe loss of bone, skin, or other soft tissue in varying combinations. Three of the 36 patients died within 48 hours of admission due to other injuries. In the remaining 33 cases there have been no non-unions, no osteomyelitis in pin tracts or in the open fractures, no amputations, one loss of length and two mal-unions. 32 people have been unqualifiedly restored to their pre-injury occupations and social and economic levels. The 33rd patient is now undergoing rehabilitation. The benign healing of severely damaged soft tissues in these cases is impressive. Equally impressive is a series of 30 consecutive cases of compound fractures[b] (most of which were severe, not relatively uncomplicated puncture wounds) which all united and none of which became infected with the use of this technique. The lack of bone and soft tissue infection is even more impressive in view of the fact that more than half of the wounds were severely contaminated due to grinding in of road dirt, industrial waste or clothing.

2. The writer's indications for the use of the crossed-pin technique in leg fractures are as follows:

   (a) Unstable segmental fractures, whether open or closed. ("Unstable" here means proven inability to maintain satisfactory reduction by purely closed means).

   (b) Extremely comminuted fractures, particularly when more than one or 1½ inches in length is so affected, either open or closed.

   (c) Any fracture of the middle three-quarters of the tibia accompanied by such severe soft tissue damage that survival of coverage, blood supply, or motor power is considered endangered and is the primary concern of the injury. In such cases the thorough stabilization of bone provided by the crossed-pin technique is more effective as a soft tissue splint than simple immobilization in plaster.

The crossed-pin technique, in the writer's opinion, has the following advantages:

   (a) Immobilization of the fracture or fractures and soft tissues is nearly as efficient as that provided by a plate. The immobilization of the soft tissue is more efficient than that provided by a simple cast or other methods of treatment which do not use some form of internal fixation.

(b)—The other two cases were among those dying of their injuries within 48 hours.

(b) There is no associated periosteal stripping to delay union and enhance the likelihood of non-union.

(c) The fracture hematoma *need not be entered* and no hardware is placed in the fracture hematoma. This avoids the risk of operative infection.

(d) Precise and dependable control of position, alignment, length, and rotation is obtained by an essentially closed, and thus safe, method. The immobilization provided is similarly effective and dependable.

(e) The technique is suitable for use when the condition of the skin prohibits open surgery on the fractures, but when some form of operative control and reduction are necessary for optimum result.

(f) A minimum of equipment, tools, and surgical know-how is needed.

3. The reader must not assume from the foregoing that any fractured tibia coming to the writer's hands will shortly bristle with pins. For each case treated by the crossed-pin technique, more than 7 have been treated by closed methods, and one by open methods, the bulk of the latter being either Lottes nails or two screws for use in transverse and spiral fractures respectively. Of the 43 legs, only two were children and in both of these the initial injury was severe enough that primary amputation was considered by others to be the treatment of choice. In children the advantages of secure control of position, rotation, length and angulation over a period of time without open surgery are obvious.

4. The writer has used this technique for 12 years. During that time there have been three complications. One was a skin slough due to inadequate anterior padding, abetted by a severe local contusion from the initial injury; the other two were union in 10° varus of subcondylar tibial fractures, one of them being accompanied by ½ inch of shortening.

5. It should be understood that the crossed-pin technique has no magical properties. The fact that during a 12 year period less than 4 patients a year in a busy orthopaedic practice were treated by the crossed-pin technique adequately demonstrates that it has been used selectively.

6. The average time from injury to first weight-bearing in the series of 33 cases is five months. This is the same as in a recent series of 150 cases of leg bone fractures analyzed at the Henry Ford Hospital by Dr. Jerome Kozak.[c] The present series should be viewed in the light that the majority of them were severe injuries with many extensive comminutions, severe compounding and severe contamination. The 150 cases analyzed by Dr. Kozak were an unselected, consecutive series, the majority of whom had closed and uncomplicated injuries. In the series reviewed by Dr. Kozak there was an incidence of a little less than 3% non-unions, while in this series there has not yet been a non-union. The writer realizes that as more cases accumulate the first

(c)—Now of Lansing, Michigan.

non-union will occur, but feels that this should not be blamed on the technique in view of the experience to date.

7. In discussing this technique over the years with colleagues, three objections have been so consistently raised that it is worth mentioning them.

   (A) Pin tract infection: This is an almost universal objection raised to the crossed-pin technique. The writer does not know the basis of this feeling but does know that in his 33 cases there have been three "wet" pin tracts (which required a week to close) and one pin tract which required a month to close. The remainder, comprising over 140 pin tracts, closed within two days after pin removal. There have been no ring sequestrae (which usually follow the use of the stylet point) and no pin tract osteomyelitis. Wet pin tracts probably result from excessive motion of soft tissues around the pins, and excessive stress on the pins following improper casting or too few pins, leading to gradual working loose at the bone-pin interfaces. *The pin is only a form of suture* and should be protected from overload in the same fashion that the suture line in a repaired tendon is protected during healing.

   (B) Non-union: This is the objection heard next in frequency and comes from those colleagues who feel that the physiologic bone absorption at the fracture line results in distraction and this in turn must result in non-union. In the cases described there have been no non-unions in spite of the fact that the majority of these cases had severe injuries. The efficient fixation secured with the crossed-pin technique is probably more important to fracture healing than physiologic bone resorption is detrimental to it.

   (C) Fracture infection: This, the next most common objection raised in the crossed-pin technique, is most mysterious since one of the basic features of the technique is that the surgeon is enabled to *bypass* the fracture hematoma completely! Thirty legs treated, containing compound fractures without subsequent infection, speak eloquently. It is worth noting an additional feature of the technique: a compound fracture which is unfixed, except by a plaster cast, has some motion at the fracture due to the shift in gravity and the pull of the various muscles at the proximal and distal joints as the patient is lying in bed, and particularly as he starts to get up on crutches. This motion is sufficient, in the writer's opinion, to impair soft tissue healing slightly and to increase the susceptibility of the tissues to infection during the first few days after injury.

CONCLUSION

A crossed-pin technique is described for managing complex, severe, tibial fractures, whether open or closed. The technique has the advantage of precise control of reduction, efficient splinting of bone and soft tissue, and surgical avoidance of fracture hematoma and periosteal stripping. The technique *in toto* is safe and reliable. Like asepsis, how-

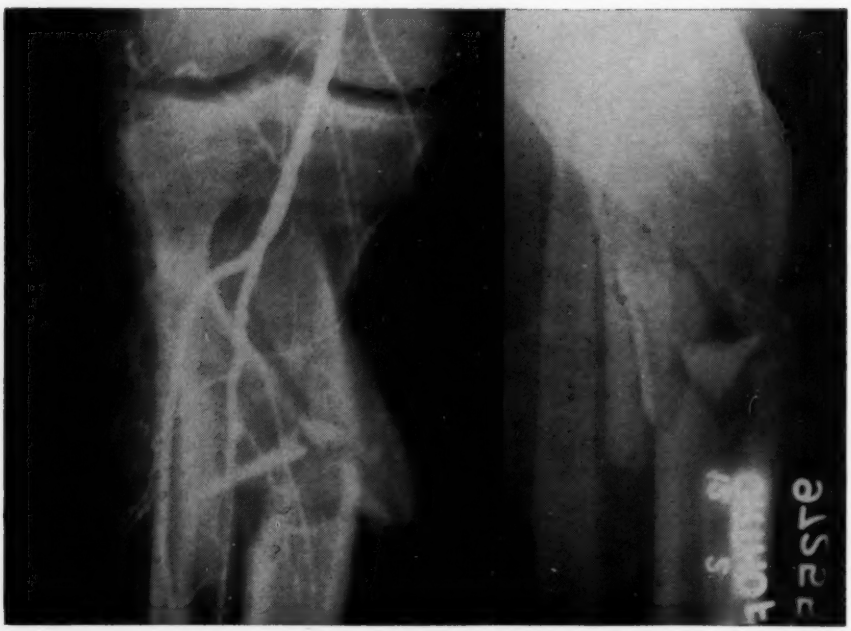
ever, it involves a ritual, and *any break in the ritual attendant to it may be dangerous.* The writer believes that the technique is among the most simple and effective presently available in treating extensively compounded, comminuted and segmental fractures of the leg. It is particularly applicable to such fractures when accompanied by severe soft tissue damage. The technique has the advantages of simplicity, efficiency, a minimum of instrumentation, devices, and tools necessary; safety from operative infection and a minimum of surgical know-how necessary for its use.

The technique has the disadvantage, in the writer's opinion, that it requires more fussiness on the part of the surgeon, and often more time, than other methods.

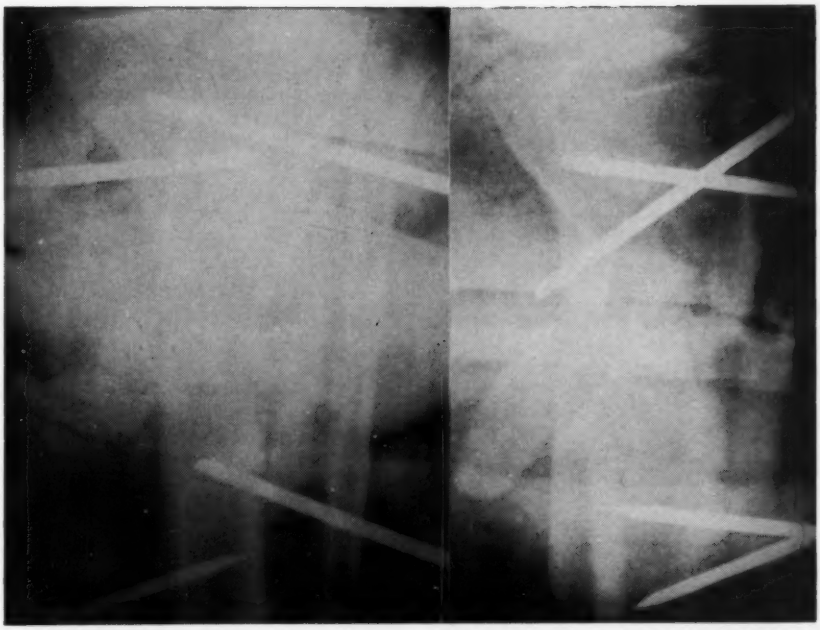
Figure 6

A 54 year old man pinned against a brick wall by a car. The driver stepped on the accelerator instead of the brake. Both bones both legs fractured, closed. Right leg treated by crossed pin technique; union and weight bearing in 4 mos.

Left leg is illustrated. Severely comminuted fracture. Pulseless foot and rapid, tremendous swelling proximal leg and knee. Arteriogram reveals occlusion of posterior tibial artery. This was explored and ligated. Partial weight bearing 5 mos., full weight bearing 7 mos. Returned to job as mechanic 10 months.



6A—Original AP and lateral views left leg; the arteriogram is illustrated on the left.



6B—AP and lateral in cast with pins in place. Note that one of the proximal pins pierces the posterior cortex. This pin drifted deeper into the leg, with loss of one plane of the proximal fragment's fixation.

6C—Result at 6 mos. when bearing partial weight. The slight shortening and varus were the result of drift of one proximal pin.

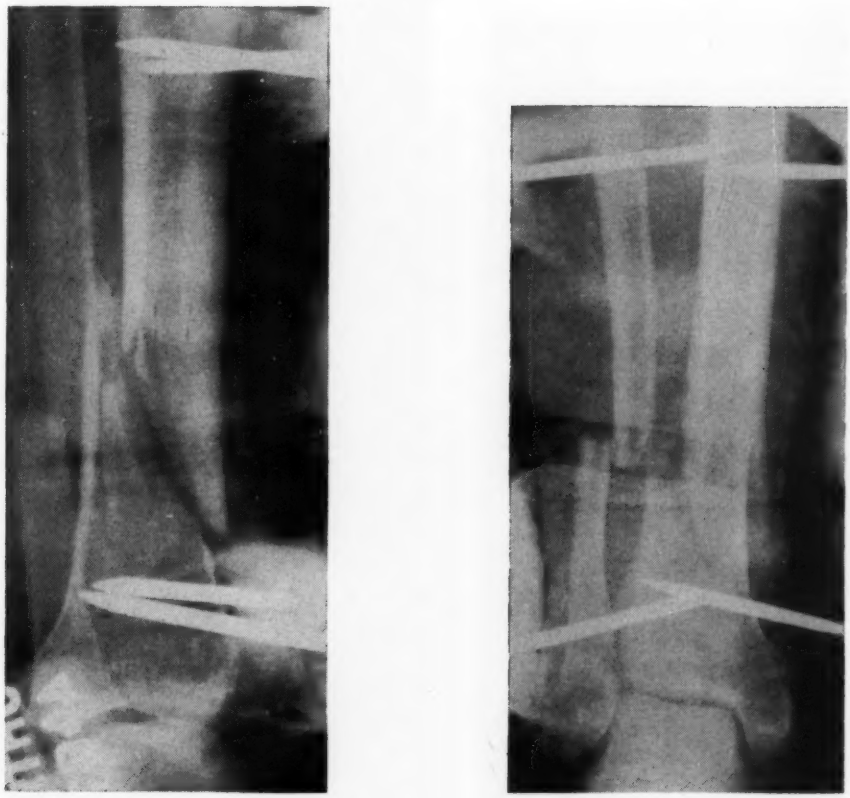
Figure 7

A 55 year old man. Compound, slightly comminuted fracture both bones right leg. The original displacement was severe. The entire distal 7 cm. of the proximal tibial fragment was completely stripped of muscle and fascial attachments and was extruding through the skin on admission to the emergency room.

Treatment: Debridement, primary closure, crossed pins.

Partial weight bearing 4 mos. Return to usual work 6 mos.

7A—Original x-rays — after leg aligned in E. R.



7B—In cast with pins, post wedging, 2 weeks.

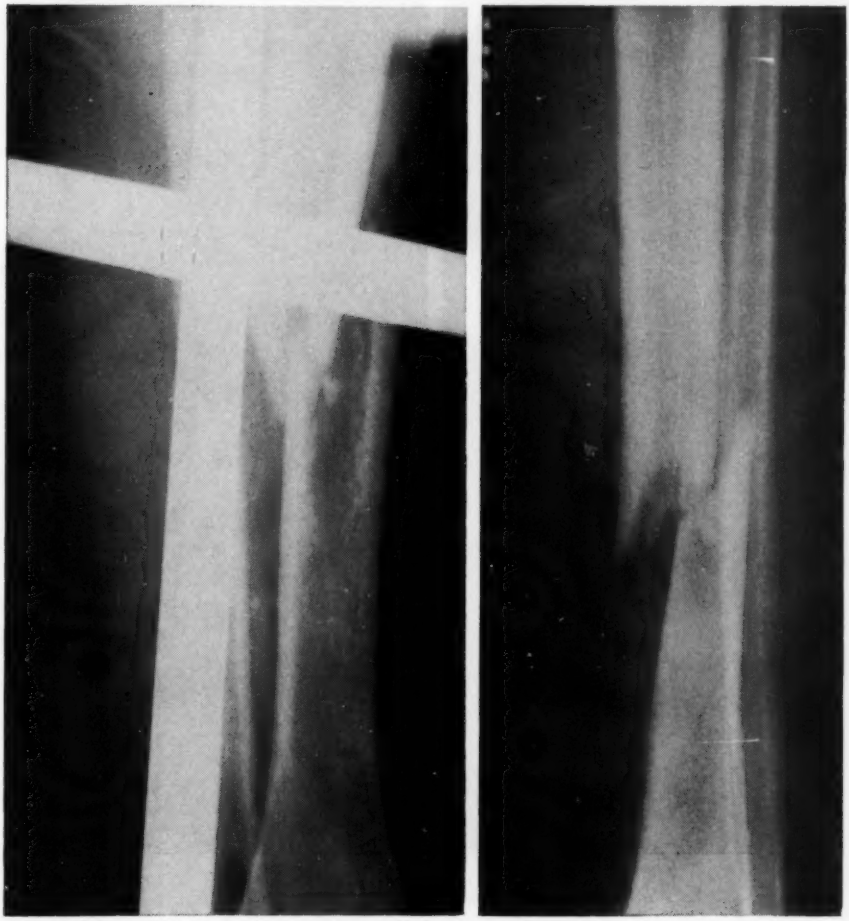
7C—One year post injury. There was no infection.

Figure 8

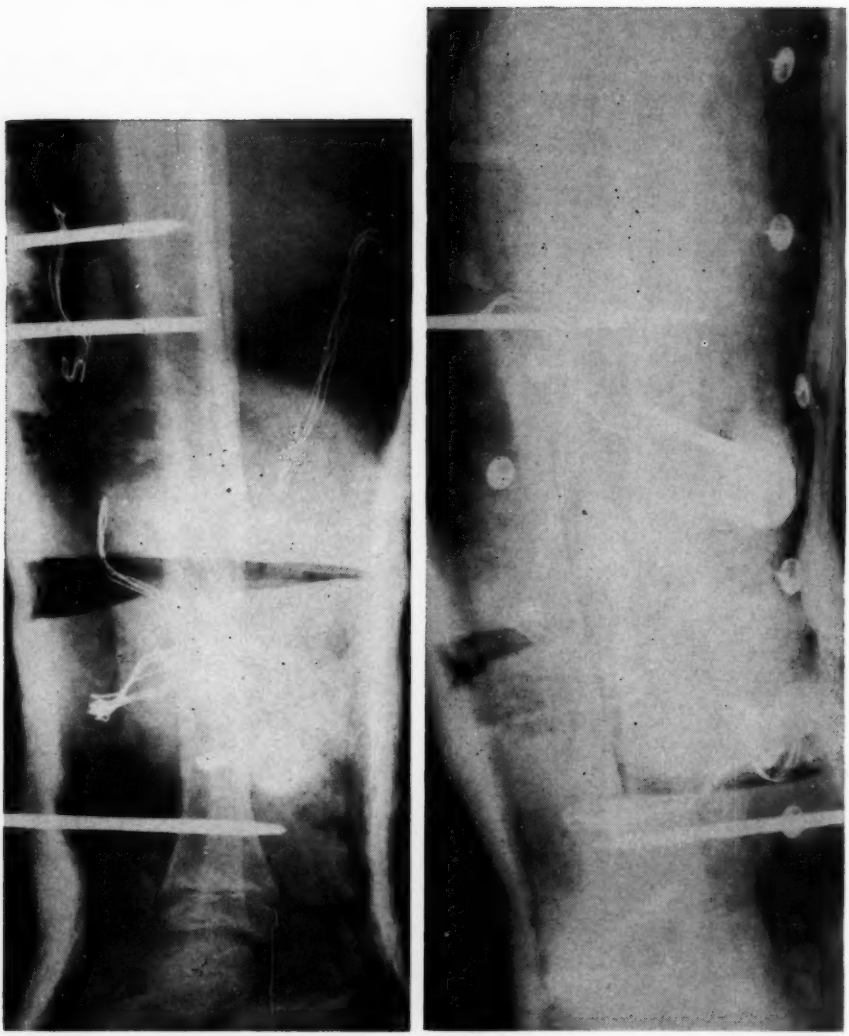
An 11 year old boy, Pedestrian hit by truck, right front wheel. Wheel was locked, leg caught in wedge between wheel and road and ground to mince meat over a 10 foot skidding distance. Compound fracture both bones leg with some of proximal part of distal fragment ground off. This is visible as a bevel on left side of tibia, right half of 8A. Soft tissues so badly mangled amputation was nearly done. Nerves damaged, road dirt ground into posterior tibial nerve, artery vein. Medial half of gastroc and soleus ground off. Part of medial malleolus ground off. Enormous full thickness skin flap extending from ankle joint line to patella and involving slightly more than half the circumference of entire leg.

The gamble was taken. Extensive debridement, loose suturing skin, crossed pins, long leg cast, antibiotics. The limb survived. Wound edge sloughs granulated in by the time fractures healed. Partial weight bearing 4 mos. Full weight bearing 5 mos. Last x-ray follow-up at 8 mos., last clinical follow up at 18 mos.

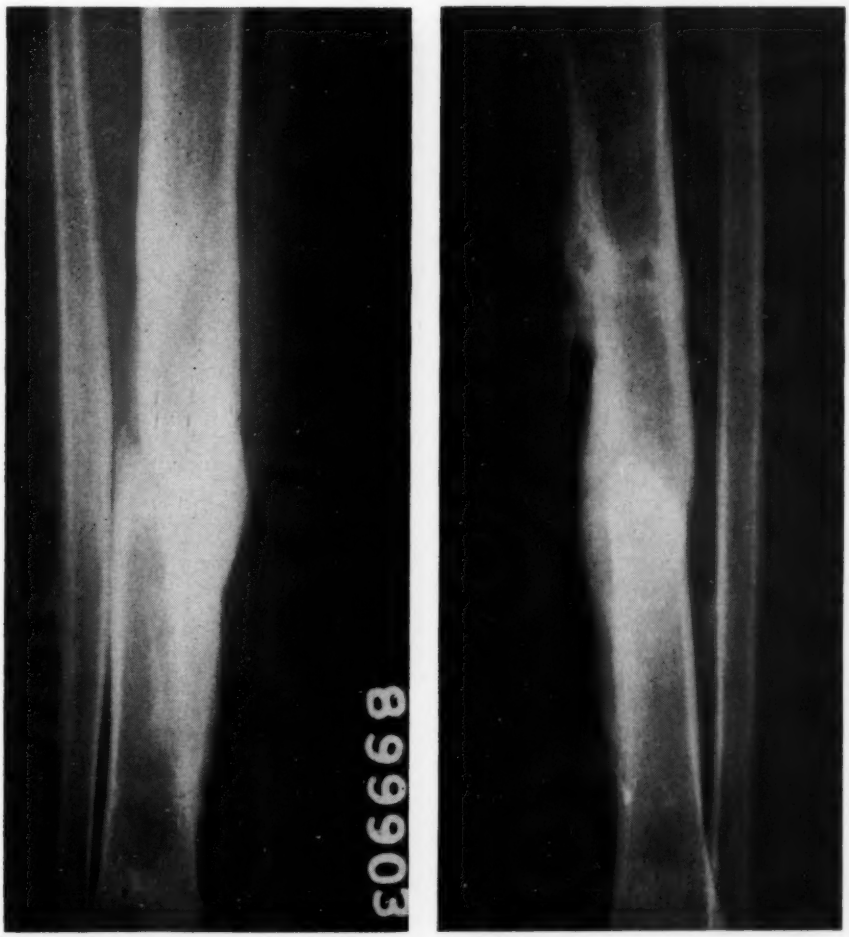
End Result: Normally functioning extremity. No infection at any time.



8A—Original films in E. R. About 6 cm. each of proximal and distal fragments were bare and periosteum ground off.



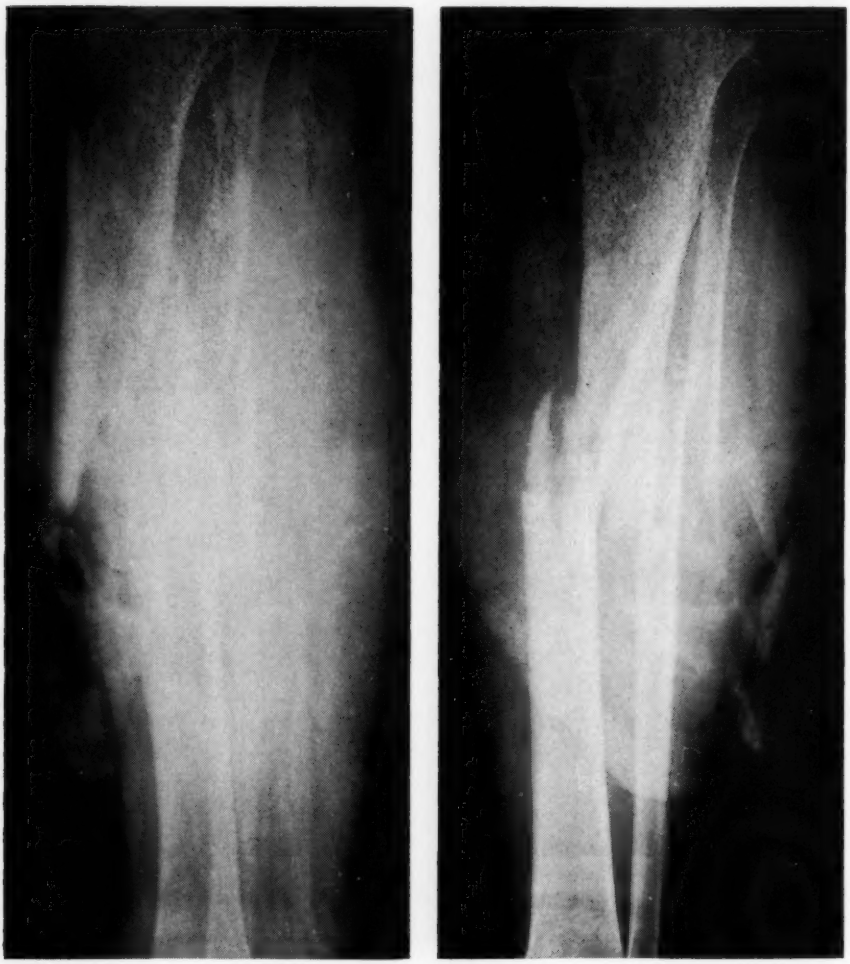
8B—2 weeks post injury. In cast with pins.



8C—8 months after injury. No infection, normal function, some calf atrophy. The atrophy disappeared in the following 10 months.

Figure 9

A 45 year old man. Leg sticking out of car window, sideswiped by another car. Comminuted fracture both bones left leg. An open fracture with 7 separate skin lacerations. When explored most of following muscles severed completely by the sharp bone ends: soleus, posterior tibial, anterior tibial, flexor hallucis longus. Neurovascular structures intact (!). Debridement, exploration, repair of motors, crossed pins. Partial weight bearing 5 mos. Full weight bearing 7 mos. Back at regular job on assembly line. Still leaves legs sticking out of windows. Normal function of extremity at 10 months.



9A—Original AP and lateral views.

9B—Lateral view in cast with pins before wedging.

9C—Lateral view after wedging. It required 2 wedges to achieve this position alignment, and length.

9D—AP and lateral views at 6 months post injury. No infection.

9E—AP and lateral views of the cast with buried pins 2 weeks post injury.

INTRODUCTION TO JOINT BIOMECHANICS*

HAROLD M. FROST, M.D.**

The application of the knowledge and discipline of other scientific fields to medical fields seldom fails to bring new understanding and advance in the diagnosis, treatment, and prevention of disease. Such advance characterizes the application of mechanical engineering to anatomy and physiology. The result of this application is the field of *biomechanics*. Biomechanics is not limited to mechanics; overtones of physical chemistry, solid state physics, metallurgy and thermodynamics appear in the field and other overtones may be expected.

In this paper a way of thinking about joints is introduced which provides some insight into the development of phenomena previously obscure in origin. Orientation of future joint research along the lines suggested should increase the yield of such research. It is hoped that the paper will provide some stimulus for such work.

BEARING ANALYSIS APPLIED TO JOINTS

LUBRICATION

A. *Lubricant:* Synovial fluid is the joint lubricant. Synovial fluid possesses the properties of viscosity, surface tension, and adhesion to the surface of hyaline cartilage. These properties are due to submicroscopic characteristics of the synovial fluid, among them being the size, shape, density, charge concentration, pH, and interactions of the various molecules in the synovial fluid. From the standpoint of lubrication, the most important molecule in the synovial fluid is that of the mucin. Alterations in the submicroscopic characteristics produce grossly measurable changes in properties such as viscosity, surface tension, and refractive index.

A lubricant functions under one of two conditions: boundary layer or hydrodynamic.

B. *Boundary Layer Lubrication:* Two bearing surfaces slide slowly upon one another. A film of lubricant is present between the bearing surfaces. The lubricant film lowers the moving friction and decreases the wear that would be present if the bearing surfaces were dry. Ideally the lubricant is strongly adherent to the bearing surfaces, forming a very thin protective coating over the surfaces.* Some wear is always present under boundary layer conditions because there is always some contact of the moving surfaces. Boundary lubricants are usually greases of high viscosity and surface tensile strength. Under boundary conditions a load limit exists beyond which the lubricant is increasingly ineffective. (Figure 1.)

*Presented at the Sixth Congress of Orthopaedics and Trauma, Mexico City, May 25, 1960. Reprinted with permission, Mexican Orthopaedic Association.

**Department of Orthopedic Surgery.

*The adhesiveness of a lubricant is usually enhanced by adding small quantities of chemically corrosive substances to the body of the lubricant.

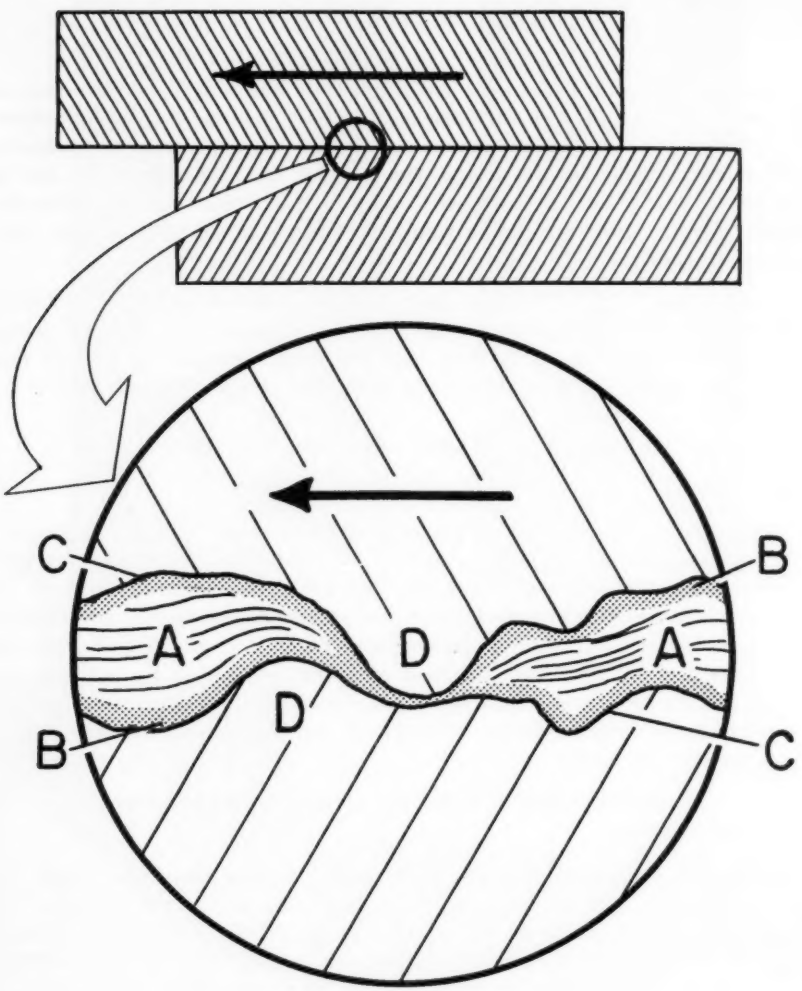


Figure 1

BOUNDARY LAYER LUBRICATION

In the top part of the figure one flat lubricated plate slides on another. In the bottom part of the figure the bearing surfaces are highly magnified and diagrammatic — the bearing surfaces are microscopically rough. As a result, most of the load is borne by small high spots, one of which is illustrated in the center of the figure. Lubricant fills the gaps between the bearing surfaces but is rubbed off where high spots touch.

A: Lubricant. B: Monolayer of molecules adherent to bearing surface. C: Bearing surface. D: High spots, or *asperities*. During motion the temperatures of the abraiding high spots become high, often high enough to melt the microscopic hills. Bearing wear is appreciable under boundary layer conditions.

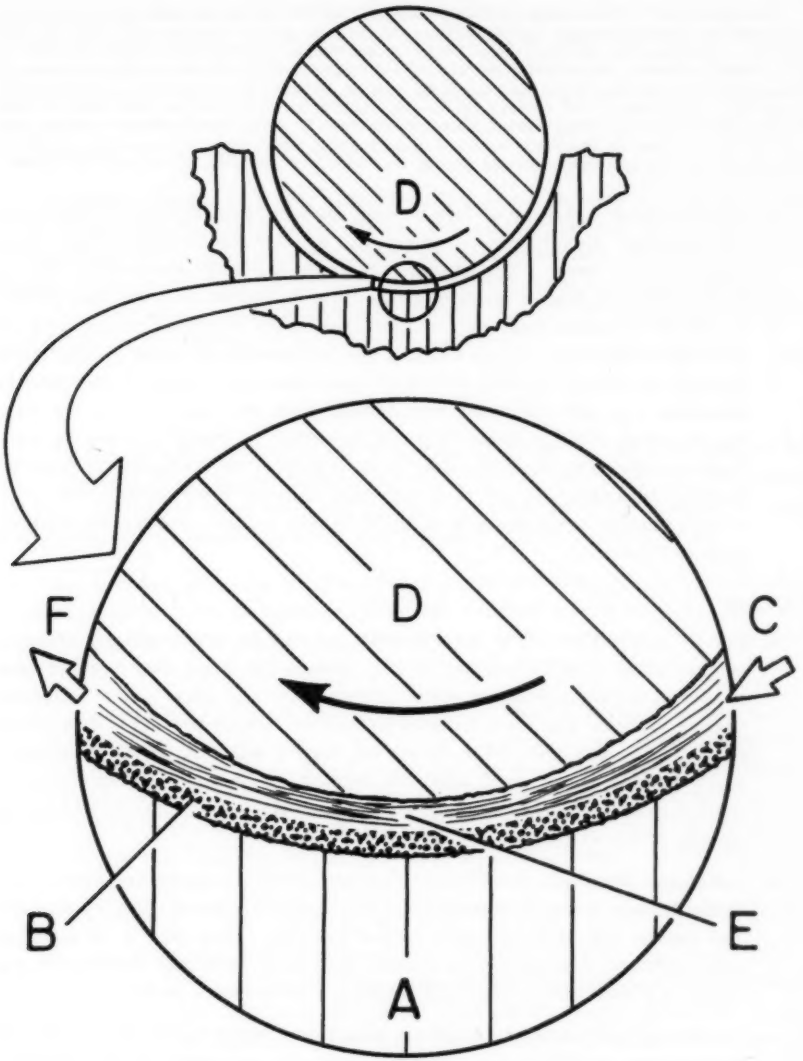


Figure 2

HYDRODYNAMIC LUBRICATION

A rotating journal is diagrammed in cross section at the top. A diagrammatic, enlarged section of this journal is depicted in the lower part of the figure and is equivalent to the function of a moving joint. Motion is from right to left, the bottom part of the bearing being stationary. A film of lubricant is pumped in from the right and is carried along by the moving surface. As the bearing surfaces approach closer the fluid pressure increases; its speed also increases. The bearing surfaces approach until the lubricant pressure equals the load on the bearing. At this point the bearing surfaces remain, moving neither closer nor farther apart. A change in load, or in bearing speed, or in lubricant viscosity, results in a corresponding change in the minimum lubricant film thickness in a bearing operating under hydrodynamic conditions.

A: Fixed part of the bearing, *bearing backing*. B: Babbitt or bearing material. C: Lubricant being forced in between moving bearing surfaces. D: Moving part of bearing: the shaft, in cross section. E: Minimum film thickness here. Under hydrodynamic conditions the minimum lubricant film thickness is always greater than the size of the largest microscopic surface irregularities on the bearing surface, so there is no touching of the bearing surfaces. As a result wear is infinitesimal. F: Lubricant is expressed from between the moving bearing surfaces, carrying away the frictional heat generated. In human joints and in machines this fluid is recirculated into the bearing again, but by different means. In machines motion is usually indirectional. In joints motion is oscillatory or reciprocal, and the lubricant expressed during, say, flexion of the knee, is returned by extension.

C. *Hydrodynamic Lubrication:* Two bearing surfaces move rapidly on each other. The lubricant, usually an oil, is pumped in between the moving surfaces under pressure. As a result, a film of lubricant forces and keeps the bearing surfaces apart. Under hydrodynamic conditions there is almost no wear and friction is reduced to a minimum. Heat is generated by the frictional resistance of the lubricant to shearing. (Figure 4). This heat must be carried away by conduction through the bearing material and/or by circulation and cooling of the lubricant. Otherwise the heat generated may damage both the lubricant and the bearing materials. This problem is more important in machines than in joints because in the latter the heat safety factor is large. Poor dissipation of frictional heat is not known as yet to cause joint damage. Some microscopic areas of heat damage could possibly occur in heavily loaded, severely osteoarthritic joints. (Figure 2.)

FRICTION

A. *Dry Bearings:* Friction is the resistance to moving one bearing surface on another under a load. In a dry bearing, *starting friction* is due to the contact and actual welding together of minute high spots — asperities — on the adjoining bearing surfaces. The force required to start the bearing moving is thus related to the *tensile* and *shear strengths* of the bearing material. *Moving friction* in a dry bearing is the work required to melt the minute high spots on the bearing surfaces as they impinge on one another and is thus related to the *melting points* of the bearing materials.

B. *Lubricated Bearings:* In lubricated bearings under boundary conditions some of the friction is due to contact (and thus wear) of the two bearing surfaces, and some is due to the viscosity of the lubricant. While heat is generated by both processes, it is smaller in amount than in dry bearings and usually produced at a slow rate so that heat dissipation is seldom a problem.

Under hydrodynamic conditions there is no contact of the bearing surfaces and thus no appreciable wear except during starts and stops. Heat is generated almost entirely from the viscosity of the lubricant which is sheared between the bearing surfaces. (Figure 4). This heat is considerable and unless dissipated in some manner, it will elevate temperatures sufficiently to damage the lubricant and the bearing.

C. *Joints:* In a normal human joint moving slowly and intermittently under load, boundary conditions exist. One can often detect the abrasion occurring during this condition as a fine crepitus under the slowly moving patella or as a self-audible grating when the neck is moved slowly in small increments.

In normal human joints moving rapidly, hydrodynamic conditions exist and wear is reduced to an insignificant level by a thick film of synovial fluid forced in between the moving joint surfaces. The means by which synovial fluid is formed, pooled, circulated and pumped in between the moving joint surfaces are complex and at present imperfectly known. Knowledge of these factors will probably improve our understanding and treatment of arthritides to a large extent.

In abnormal joints, such as in chondromalacia, in a joint made irregular by fracture, or in severely osteoarthritic joints, the capacity of the lubricant to protect the joint surfaces from touching is exceeded, even under hydrodynamic conditions. Contact of the two surfaces occurs, large particles of the bearing surfaces are gouged or torn out of each surface during motion, and large amounts of heat are generated in physically small volumes of material. Wear is severe and rapid.

BEARING MATERIAL

The hyaline cartilage lining joints is comparable to the Babbitt of a machine bearing. (Figures 2, 3, 7). It must possess five properties to function well. Hyaline cartilage is a poor structural material and is not intended to provide structural strength or stability. It provides a low-friction, low-wear, self repairing gliding mechanism.

The requisite properties of a bearing material are smoothness, adhesion to the lubricant, absorption of the lubricant, resistance to shear greater than any shear which may be transmitted to the bearing by the lubricant under normal operating conditions, and sufficient surface area to carry the loads placed on the bearing.

A. *Smoothness:* Under the magnification of the electron microscope the apparently smooth surface of hyaline cartilage in a normal joint is resolved into jagged edges of bare collagen fibers projecting into the joint space. These high spots cause contact and some wear under boundary conditions in normal joints. Under hydrodynamic conditions the lubricant film is much thicker than the height of the largest surface protuberance and no contact or significant wear occurs. When surfaces are rough to the unaided eye the condition is already serious and wear is rapid. Surface smoothness is essential to minimize wear.

B. *Adhesion:* Physicochemical interaction between cartilage substance and the synovial fluid molecules is responsible for the fact that normally the two are quite adherent and it is difficult to "rub off" the mucin molecules from the cartilage. The nature of the forces responsible for this adhesion are such that relatively small disturbances in composition or physical characteristics could affect the adhesiveness considerably. At present there is no positive evidence that this occurs in man: it has not been sought for.

C. *Absorption:* The construction of the hyaline cartilage is such that the synovial fluid is absorbed by the cartilage. The cartilage "soaks up" some of the lubricant as a blotter soaks up ink. In situations where insufficient supply of lubricant is carried in between the joint surfaces this absorbed fluid may be squeezed out and act as a temporary supply.

D. *Shear Strength:* The hyaline cartilage covering joint surfaces is composed of bundles of collagen embedded in a cement substance, much as bundles of string might be embedded in gelatin. The collagen is strong, flexible, but not very elastic, while the cement substance is quite elastic but not strong. The collagen fibers come directly out of the subchondral bone and overlying calcified cartilage, course through the thickness of the cartilaginous covering on the subchondral bone and come to lie in largely tangential fashion at the joint surfaces. The cartilage is accordingly strongly attached to the subchondral bone and is strongly resistant to being plucked away from or sheared off from the subchondral bone. The feltwork of parallel fibers at the joint surface makes the cartilage difficult to split apart. (Figure 3). When this surface layer of tangential fibers is worn off, vertical splits may develop in the cartilage. This is the initial pathology in the condition known as chondromalacia.

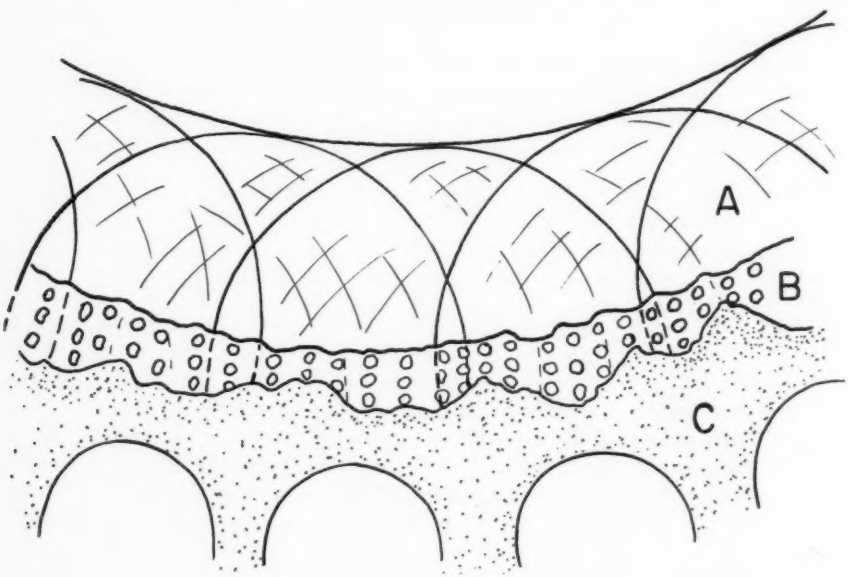


Figure 3

Diagrammatic, enlarged longitudinal section of a joint. Layer (A) is hyaline cartilage; the joint cavity is at the top. The arching, dark lines represent the direction of collagen bundles. These bundles comprise a major part of hyaline cartilage. It will be seen that at the joint surface the bundles are tangential, but at the base they emerge radially to the joint surface. Layer (B) is the zone of calcified cartilage containing the lacunae of degenerating and degenerated chondrocytes. The upper surface of this layer is slightly irregular, the lower surface markedly so. These irregularities make it almost impossible to shear the layers apart (see Figure 5), under normal circumstances and in the presence of compressive load. Layer (C) is the subchondral bone containing an arched series of trabeculae which take load from the cartilage and distribute it to the metaphyseal cancellous bone.

The shear strength of hyaline cartilage is due to the collagen in the cartilage and under normal circumstances is more than sufficient. (Figures

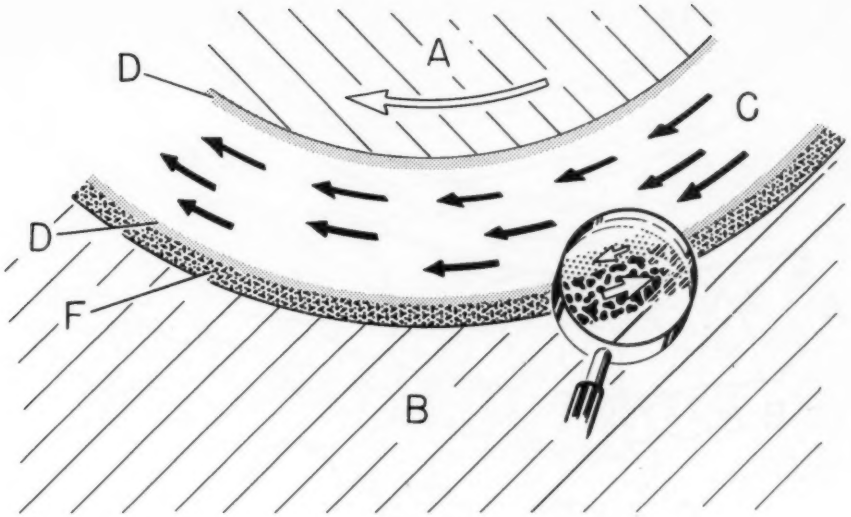


Figure 4

Diagrammatic representation of behavior of a lubricant between moving bearing surfaces. The moving bearing surface is above (A), the fixed one below (B), and the direction of motion is as diagrammed. Lubricant enters from the right (C). A thin film of lubricant molecules adheres to each bearing surface (D) and remains attached thereto. Each successive layer of lubricant moves on the preceding layer of lubricant under the drag from the moving bearing surface. This moving of layers of lubricant on each other is *shear;* the drag, or fluid friction, is *viscosity,* or resistance to shear. A shearing force is transmitted from the lubricant to the bearing surfaces and is outlined by the magnifying glass. When enough shearing force is generated the bearing material (F) can be stripped from the bearing backing (B).

4, 5, 6). When surface roughness exists in the joint, however, the strength of the collagen may be exceeded and bits of cartilage plucked out of or shorn off from the subchondral bone during motion. In such a joint the heavier the load, the faster and more severe the wear and thus the greater the symptoms. It is for this reason that progressive resistance excercises are not the best prescription for the patient with patellar chondromalacia.

E. *Bearing Area:* The bearing area will be elaborated on next and deserves separate consideration.

BEARING SHAPE

From anatomy texts one might conclude that nature uses diverse bearing shapes having no common features. Nevertheless, it has been found that diarthrodial joints do have two design features in common that are not apparent at first glance but that are of considerable physiological significance.

A. *Fluid Wedge:* Under no-load conditions the diarthrodial joints do not have accurately mating surfaces. Their shape is such that there is a central, small area of contact* but at the periphery of the joint an open, wedge-shaped space exists. The gap in this wedge is usually filled with synovial fluid. When motion

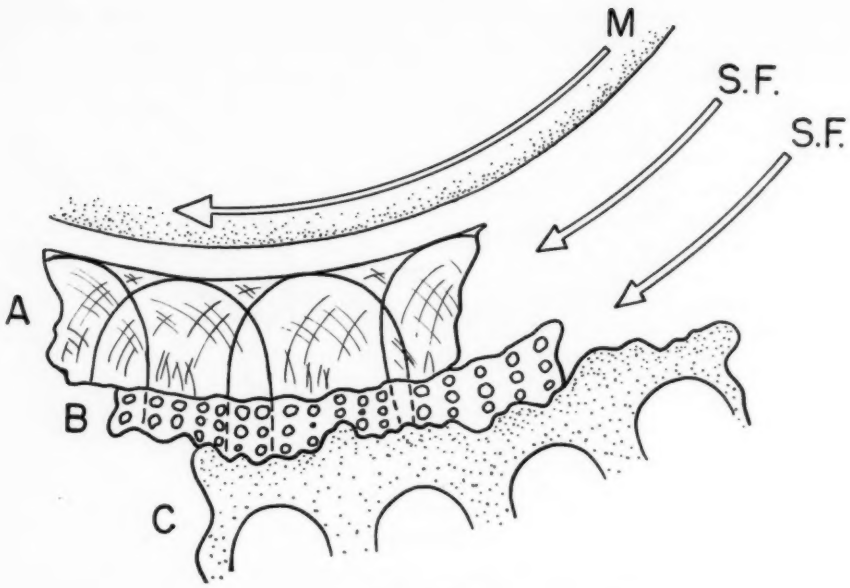


Figure 5

The arrows (SF) represent a shearing force created by motion of the joint surfaces. The upper member of the joint and its motion are represented by arrow (M). The viscosity of the synovial fluid is responsible for transmission of shearing force from the moving joint surface to the stationary joint surface. If the cohesion of hyaline cartilage (A) to calcified cartilage (B), or of calcified cartilage (B) to subchondral bone (C), were inadequate then the shearing force which *always* accompanies joint motion would produce the shear failure and displacement shown.

occurs the volume of fluid in the wedge is carried between the moving surfaces and forces them apart, causing hydrodynamic conditions. The fluid wedge, adhering to the cartilage surface, and possessing a fair viscosity, is an essential part of the "pump" that, with the aid of motion, creates hydrodynamic lubrication of human joints. In extreme cases such as the knee, where the wedge at the joint periphery is large, a meniscus occupies the gap, maintains an unbroken fluid wedge, minimizes turbulence which would break the fluid wedge up, and is flexible enough to adapt to varying positions of the joint. (Figures 2, 7).

B. *Variable Bearing Area:* The elastic flexibility of the hyaline cartilage, subchondral and metaphyseal cancellous bone which support the hyaline cartilage, and metaphyseal cortex which supports the entire joint complex, is graduated.** The structures were listed in order of decreasing elasticity. (Figure 9). As a result of their elasticity the central area of closest contact in the resting, unloaded joint progressively enlarges as the load increases. In man, therefore, the surface area of the bearing is variable. The bearing area is dependent on

*Contact does not necessarily mean touching. Usually a thin film of synovial fluid prevents actual contact over any significant area of the normal joint.

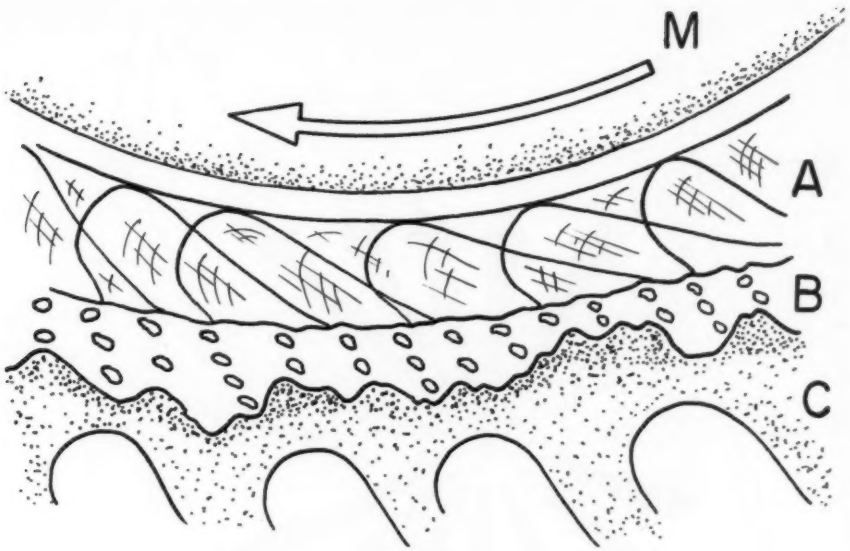


Figure 6

Now we diagram the deformation or *strain* produced in the hyaline cartilage, calcified cartilage and subchondral bone by the shearing force generated by joint motion. Compare with Figure 1. The shearing force causes the whole joint surface to give way to the left. The amount of strain is exaggerated, but some strain *always* occurs with the shearing force of joint motion.

and varied by changes in the load. This is a unique arrangement in bearings. (Figures 6, 8A, 8B).

BEARING BACKING

The hyaline cartilage covering the joint surfaces serves the functions of lubrication. Structurally it is too weak for any sizable load, just as the Babbitt in the bearings of a machine is too weak for any large load. Some backing or supporting structure must be provided. In man the bearing backing may be considered in three parts: the subchondral bone, metaphyseal cancellous bone, and metaphyseal cortex.

A. *Subchondral bone:* The subchondral bone microscopically is a nearly continuous but rather rough, thin plate of bone underlying the calcified cartilage at the base of the hyaline cartilage layer. The external roughness probably adds resistance to shear between the zone of calcified cartilage and the subchondral bone. The subchondral bone is quite flexible and must itself be supported. (Figure 3).

B. *Metaphyseal Cancellous Bone:* A system of trabecular archways originating on the under side of the subchondral cortex takes the compressive, tensile and

**All structural materials are elastic, differing only in the degree of elasticity. *All* structural materials yield under a load, no matter how small. The yield is known to the engineer as *strain.* Normal human bone and cartilage undergo considerable elastic strain in response to physiologic loads, a fact not apparent in the static view of the dissecting room.

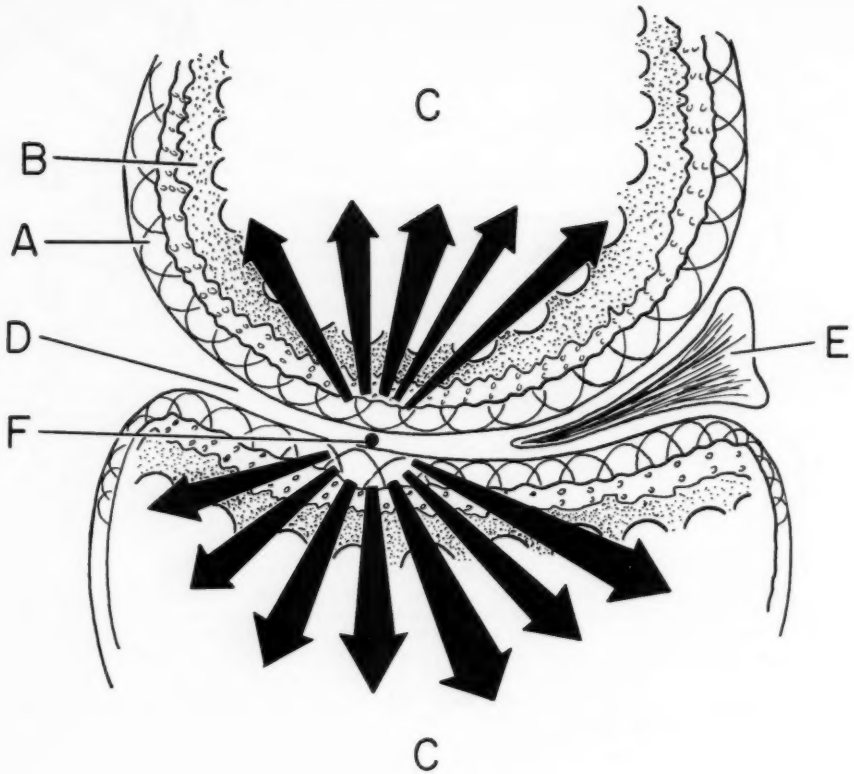


Figure 7

A diagrammatic joint (A) Hyaline Cartilage; (B) Subchondral bone; (C) Metaphyseal cancellous bone — not diagrammed. At (D) a wedge-shaped space at the periphery of the joint exists and normally is filled with synovial fluid — the *fluid wedge*. At (E) the peripheral wedge shaped gap is so large that nature fills it with a filler — which is known anatomically as the meniscus. Under resting conditions or with small loads only the central area, (F) of the joint is actually bearing. The load at the bearing area is distributed by the subchondral cancellous bone in the manner diagrammed by the arrows.

shear loads transmitted to the subchondral cortex and distributes them to the widest possible area of the metaphyseal cortex. Some elastic flexibility is necessary for this function.

The elastic flexibility of the whole cartilage-metaphyseal bone complex has already been referred to as the mechanism responsible for the variable bearing area in man which is controlled by the load. This flexibility also aids in distributing and equalizing loads and in eliminating any local zone on the bearing surface which might carry too much load.

C. *Cortex:* The metaphyseal cortex, quite thin at the margin of a diarthrodial joint, gradually lessens in diameter, and thus cross section area, but increases in

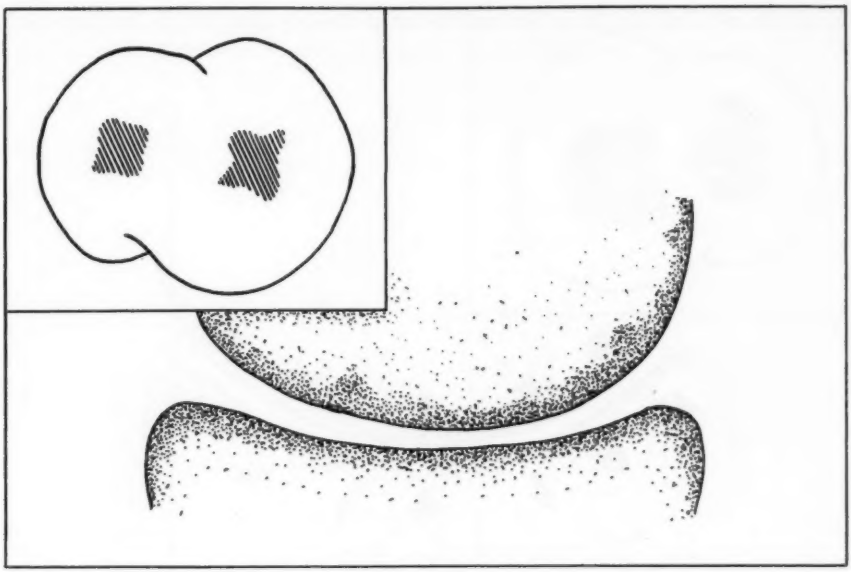


Figure 8a

The tibial side of the knee joint is seen as it would appear if one were looking down on it. The shaded areas at upper left represent the amount of bearing area in close apposition and bearing load at rest or with small loads. The majority of the joint surface is not bearing. In the lower part of the figure the peripheral wedge is illustrated for no-load or light load conditions as it would appear on a longitudinal section through the joint.

thickness as the diaphysis is approached. This is the final touch in the design of the joint mechanism and is the manner in which the apparently incompatible demands of mobility, adaptability, and structural stability are satisfied. Elasticity gradually tapers off from the joint surface to mid-diaphysis.*

D. One of the necessary properties of the bearing backing has been repeatedly referred to: *Elasticity*. Other properties are also needed for proper functioning of the bearing as a whole. These properties include sufficient strength, fatigue resistance, and heat dissipation. These are separate matters which need not be gone into in detail here.

SUMMARY OF BEARING THEORY APPLIED TO JOINTS

A series of requisite properties or materials will be listed separately, although they are often interdependent.

Lubricant: The synovial fluid must adhere to the bearing surfaces, be present in adequate supply and possess relatively constant viscosity and surface tension. The synovial fluid must meet the harsh demand of subserving both boundary layer and

*The energy absorbing capacity and damping capacity of the metaphyseal structures are also important functions but are not discussed.

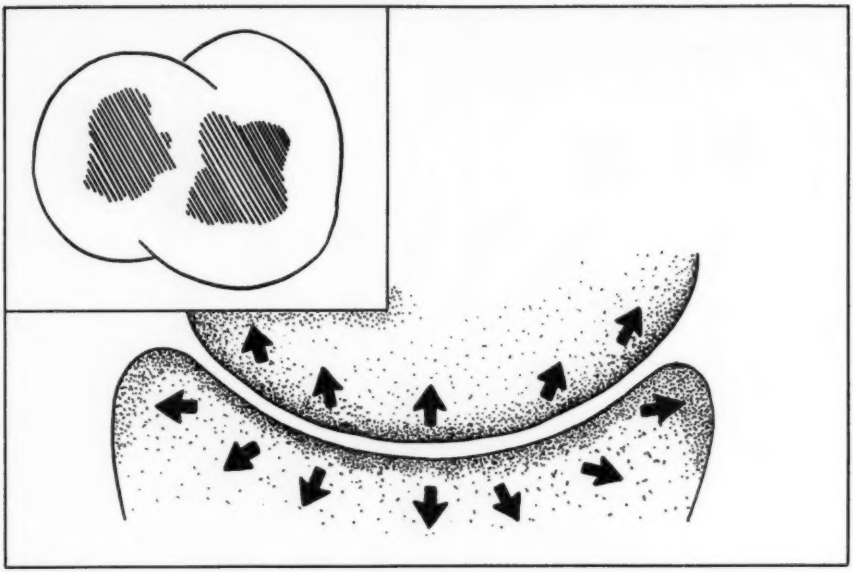


Figure 8b

The same as in 8A but now under heavy load. The shaded area in the upper left part of the figure again represents the bearing area and is seen to have enlarged considerably. In the lower part of the figure the arrows show, in longitudinal section through the joint, how the material in the metaphysis must be elastically displaced to permit increase in the bearing area under increase in load. It can be seen that failure to adjust bearing area to load could lead to severe overload on the small bearing area in Figure 8A under heavy load conditions. Any situation which produces an abnormal protuberance in the joint surface, or which reduced normal subchondral cancellous elastic flexibility can produce such overload and lead to degenerative arthritis.

hydrodynamic lubrication while simultaneously carrying nutrient materials to the cartilage for use by chondrocytes and carrying away catabolites. Wear and friction must be minimized and frictional heat must be carried away and dissipated.

Bearing Surface: This must be very smooth to minimize friction and wear. The maximum roughness must be of lesser order than the minimum thickness of the lubricant film.

Absorption of Lubricant: The bearing material should absorb some lubricant for use in occasional "dry" periods when lubricant is not being pumped in between the bearing surfaces.

Lubricant Pump: A mechanism is required to force synovial fluid in between the moving joint surfaces. This "pump" arises from a combination of circumstances: the relatively high viscosity of the synovial fluid, its high adhesiveness to the joint surfaces, the fluid wedge at the periphery of the diarthrodial joints, and the oscillatory rather than continuous nature of joint motion, so that lubricant expressed from between the joint surfaces is returned by the next motion, which *must* be in the opposite direction. In some joints there is also an arrangement of tendon and muscle such that surplus

synovial fluid in the joint recesses is forced into the middle of the joint by muscle action, ensuring that the synovial fluid does not pool uselessly.

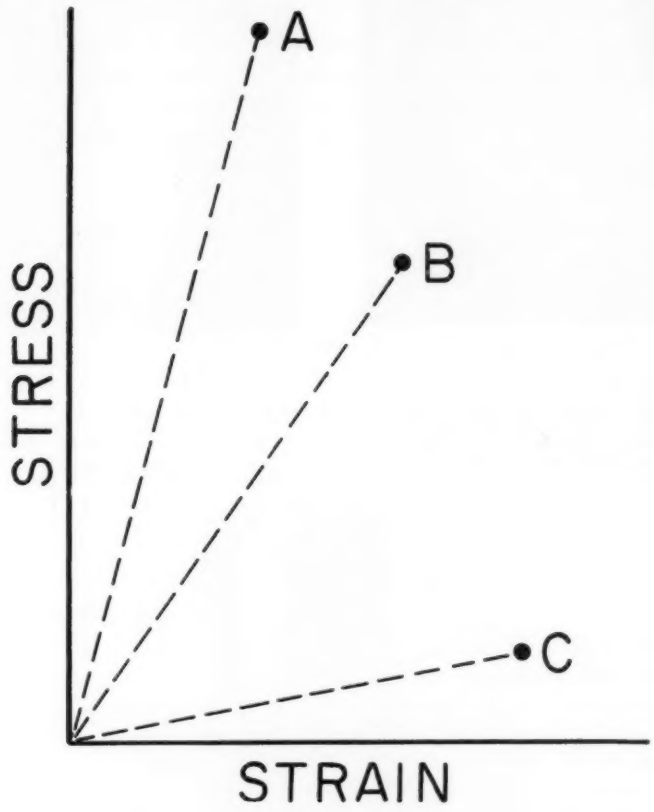


Figure 9

Stress (resistance to applied force or load) plotted against strain (deformation or giving away), diagrammatic. Comparison of qualities of cortical bone (A), cancellous bone (B), and hyaline cartilage (C).

Variable Bearing Area: This is produced by elastic flexibility of the tissues composing the joint. The flexibility is tapered, being maximal in the bearing material and minimal in the diaphysis. The resulting elastic flexibility is such that the load placed across a joint determines the bearing area of the joint. The bearing area is minimal at rest and maximal at high load. For any given set of bearing conditions there is an optimum bearing size, and varying the load on the bearing varies the optimum bearing area similarly. Our joints have engineered into them the capacity to make instantaneous selection of the best compromise between the conflicting requirements of wear minimization and load carrying capacity.

Figure 10a

AP and lateral views of left knee of a 60 year old man with osteopetrosis. Marked narrowing of the patellofemoral and medial tibiofemoral joints are seen. There are large osteophytes at the medial joint margin.

Figure 10b

Clinically there is much crepitus but minor symptoms. The opposite knee is similarly affected clinically and roentgenographically.

This is an unusual cause of alteration in the elasticity of the joint-metaphyseal complex mentioned in the text.

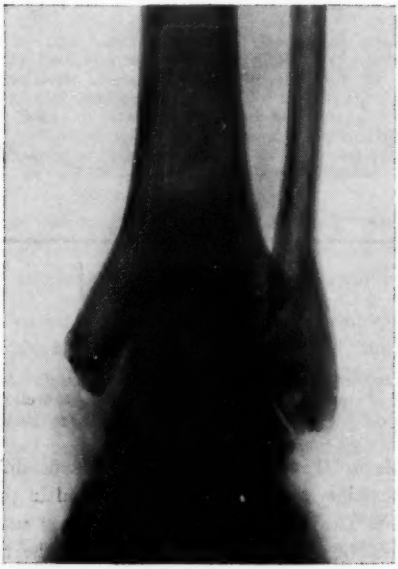


Figure 11

AP x-ray view of ankle of 34 year old woman. Ankle pain, warmth, tenderness and limitation of active and passive motion for 3 mos. Diagnosis of rheumatoid arthritis substantiated by the usual tests, by involvement of other joints subsequently, and by subsequent course.

There is marked narrowing of the tibiotalar joint. This narrowing is due to wear, not to pannus. The wear in turn results from a disturbance in the synovial fluid, the hyaline cartilage, or both. The disturbance must be such that lubricating efficiency is lowered.

The elastic flexibility of hyaline cartilage should depend in part on the metabolic activity of the chondrocytes buried in it, and so in turn on the various local and systemic factors which might affect the chondrocyte metabolism. It should depend also on the factors affecting the synovial fluid.

The elastic flexibilty of the bone which forms the backing to the cartilage must depend on blood supply, trauma, neoplasm, and other factors, some of which probably have not yet been recognized, in addition to the known local and systemic factors which affect osteoblastic activity. Too much bone backing up the cartilage would make the bearing mechanism too rigid, while too little would make it too flexible.

Strength of cartilage, subchondral bone and their mutual bonds: During an active life large tensile, compressive and shear stresses are developed in the various components of joints which have been discussed. Under normal conditions the strength of the materials is sufficient to prevent failure under isolated loads. Under abnormal conditions, however, failure may occur. For example, in chondromalacia pieces of cartilage are plucked off from the subchondral bone, and in osteoarthritis pieces of bone are sheared off or plucked out of the main body of the joint.

Fatigue limit of joint tissues: We are just beginning to appreciate that living tissues experience fatigue in the sense used by structural engineers. Collagen fibers may fail after a certain number of cyclic applications of load, as may bone trabeculae, or islands of extra-Haversian bone, or whole bones. March fractures, spontaneous heel cord ruptures and Looser's zones are specific examples of gross fatigue failures, while microscopic cracks in living bone are an example of microscopic fatigue failures. The fatigue limit of joint tissues becomes a problem when protective and repair mechanisms are impaired, as in neuropathic joints.

Self repairing feature of joints: The structural materials of which joints are made are alive and possess the capacity to repair themselves. Nature has made good use of this capacity. The various parts of a joint are designed for a limited lifetime, which does not approach the lifetime of the whole organism. The Engineer apparently decided that, rather than make joints very large, very strong, and very durable so that they would last three score and ten, he would make them light, streamlined, and with parts designed for a few years only. He added to this a continuous replacement of worn material as it develops. Both cartilage and bone wear and/or fatigue and both are replaced or repaired by various mechanisms during life. Retardation of this normal repair process leads in turn to cumulatively evident joint disease just as surely as acceleration of wear does so.

DISCUSSION

We may now consider briefly some situations which may be explainable by the foregoing material.

A. *Alteration in synovial fluid quality:* It is well known that in many cases of rheumatoid arthritis the first x-ray sign is a remarkably even narrowing of the affected joint spaces. This is seen before the manifestation of destruction, marginal notching, or the appearance of pannus. The narrowing of the joint space is due to wearing away of the cartilaginous surfaces. This in turn must be

due to loss of lubricating efficiency. Since it is not due to roughness of the joint or pannus, it must be loss of lubricity of the synovial fluid or loss of elasticity of the hyaline cartilage cement substance or both that is responsible.

A similar situation occurs occasionally in cases of epiphyseolisthesis. In the cases being considered the joint space melts away on x-ray. This loss of joint space is not related to treatment, function, or degree or slip, and so must be due to a disturbance in the quality of the lubricant, or the quality of the hyaline cartilage or both.

B. *Loss of the fluid wedge:* It is known that many years following meniscectomy a degenerative arthritis may appear and that the presence of detectable joint damage at the time of arthrotomy is not necessary for it to develop. It has been suggested, and the writer agrees, that the likely cause is failure of an adequate meniscus to regenerate after surgery, and so loss of the normal fluid wedge* which assures hydrodynamic lubricating conditions. The answer would seem to be to remove enough of the original meniscus so that a raw rim is produced which can regenerate a new meniscus.

C. *Roughness of the joint surfaces:* Familiarity with this situation is such that little need be said about it. Even the slightest step-off or irregularity in a joint surface following a fracture may be sufficient to cause severe wear and result in traumatic arthritis. Treatment should be designed to prevent or correct step-off from fractures that enter joints.

F. *Alteration in subchondral elasticity:* When too much bone in the subchondral area of a joint occurs, the elasticity of this area is markedly reduced. The overlying bearing surfaces will be overloaded under heavy loads, taxing the capacity of the bearing complex. Excessive wear may result leading first to a chondromalacia, then to a degenerative arthritis. A case is illustrated in which the cause of the excess metaphyseal bone is Osteopetrosis. Clinically there is severe tibiofemoral chondromalacia, but almost no patello-femoral chondromalacia.

Similar examples may be found when other lesions inducing appreciable osteoblastic response (such as osteomyelitis, or healing comminuted fractures) occur in metaphyseal bone close to a joint surface.

G. *Insufficient bearing area:* When part of a joint's bearing area is lost, as by depressed fracture, or when genu varum follows malunion of a femoral shaft fracture, the result is that too much load is placed on a restricted bearing area. Rapid wear results and may lead to a degenerative arthritis.

CONCLUSION

Enough. Many more possibilities could be considered and debated. The paper has served its purpose if it starts the reader thinking about joints and their diseases in terms of bearings as well as (not instead of) living tissue. It has doubly served its purpose if

*The loss is caused by a marked local increase in turbulence, in theory at least.

someone has been stimulated to test the functional model outlined. A mechanical engineer's view of joint physiology will not supplant the physiologist's view, but it should complement it. From the brief examples given, it can be seen that the model does explain some phenomena otherwise difficult to understand.

GLOSSARY

Bearing: The complex of the lubricant between two moving bearing surfaces, the bearing surfaces, the bearing backing, and any associated structures.

Elasticity: The ability to deform or yield under load and to return to the original dimensions and shape after removal of the load.

Fatigue: The gradual onset of failure of a part subjected to repeated loads, none of which exceed the design limits of the structural material in question. Microscopic cracks appear in a material that is developing a fatigue failure. The cracks gradually grow until so little material remains intact that a single, minor load may lead to complete failure. Some materials are very sensitive to fatigue, others insensitive. Fatigue is influenced by corrosion, composition of the material, heat treatment, work hardening, nicks, scratches, notches, manner of clamping and other factors.

Friction: The resistance to motion of two bearing surfaces being moved on each other. *Starting friction:* The force required to begin motion of two bearing surfaces at rest. Starting friction is always larger than *moving friction,* which is the force required to continue motion once started.

Load: force or weight applied to a part.

Lubricant: A substance designed to decrease wear and lower starting and moving friction. Lubricants are usually liquids but in special circumstances may be gases or solids. The design of lubricants is an extensive and highly specialized field. A lubricant must be designed for each combination of unit bearing load, bearing speed, bearing and lubricant temperature, bearing material, rate and manner of lubricant circulation, rate of heat dissipation, physical and chemical environment.

Strain: The deformation of a material under load. The stretching of a rubber band is strain; the force required to strain (stretch) it = load.

Stress: The resistance developed in the interior of a substance in response to an applied load. There are three general types of stress. *Tensile stress* is a pulling apart. *Compressive stress* is a pushing together. *Shear stress* is a resistance to sliding of one surface on another, for example, a brick over the top of a table.

Surface tension: The force in a thin film or at the surface of a substance which acts to contain it. It is usually measured by an instrument which makes a film and then measures the force required to break the film.

Viscosity: Fluid friction. The lubricant between two bearing surfaces is subjected to shearing stress when the bearing surfaces are moving. The shearing stress is the resistance to being sheared, and is experienced by the engine turning the shaft of the bearing as lost work. The work done on the lubricant is converted to heat in the lubricant. Some of this heat is transmitted to the bearing surface, the remainder is carried away by the circulating lubricant. If the heat dissipating means fails, overheating will occur with damage to both bearing and lubricant. As the load on the bearing increases, or as the speed of motion of one surface on the other increases, an increasing amount of shear load is transferred to the bearing material because of the viscosity of the lubricant. If improperly designed, this shear load may strip the bearing off the backing material, leading to failure of the bearing.

ACUTE CHOLECYSTITIS IN CHILDREN

NORRIS GILFILLAN, M.D.* AND JOHN H. WYLIE, JR., M.D.*

Acute cholecystitis and cholelithiasis do not follow the same pattern in children that is usually seen in adults. The diagnosis is often obscure since the usual findings of fatty food intolerance, body build, age, and sex are rarely if ever associated with this disease in childhood. If we draw from the experience of Glenn[1], Gross[2], Ulin[3], and others, we find the following data most pertinent.

Most cases of acute cholecystitis in childhood are associated with acute systemic diseases such as acute hemolytic streptococcal septicemia, typhoid fever, erysipelas, and scarlet fever. Schwegman[4] pointed out that a certain incidence of acute cholecystitis is seen in adults following unrelated surgical procedures. The factors present in the post operative period in adults may well be the same as those seen in childhood cholecystitis complicating acute systemic disease. Decreased or absent oral food intake and dehydration contribute to biliary stasis, concentration of the bile, and a diminished hormonal stimulation of gallbladder contractions. The use of narcotics to control pain may further aggravate this problem by producing sphincter spasm.

The incidence of cholelithiasis in childhood cholecystitis is 57%-69% as compared with an incidence of 93%-95% in this disease in adults. Over 60% of the childhood stones are of the pure pigment variety and most are associated with a demonstrable hemolytic disorder.

A history of jaundice has been reported in 26%-43% of children with gallbladder disease. It would seem that extra hepatic obstructive jaundice associated with cholecystitis in childhood is not commonly related to stones and is more likely the result of cholangitis and periductal edema. If we consider children with a recent history of jaundice, only 8% will reveal common duct stones while 48% of adults will have common duct stones. In 326 cases of primary gallbladder disease in children, Ulin[3] found only 6% with common duct stones. Gerrish[5], in 35 cases of jaundice in children from 6 months to 12 years of age, found 33 cases of intra-hepatic disease and only 2 cases of extra-hepatic ductal obstruction — both of these due to pancreatitis. Jaundice per se, particularly in the absence of stones in the gallbladder, does not appear to be nearly as strong an indication for common duct exploration in children as it is in the adult variety of the disease.

The rather typical history and somatic pain patterns seen in the adults are not found in children with any consistency. The only facet of the usual historical information which may be helpful is the familial history of gallbladder disease. The usual ratio of females to males of 4:1 in adults changes to 2:3 in children.

The case summary that follows illustrates some of the points that have been discussed.

A. J. #988391 was a three year old Negro male who had been perfectly well until 6 days prior to admission. At that time he began to appear somewhat lethargic. The following day he was anorexic, whined a good deal, and was noted to have some

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enlarged glands in the neck. Three days prior to admission he was treated by his family physician because of the onset of a rash on the abdomen and the soles of the feet. This was diagnosed as measles. At that time his temperature was 102°F.

The following day he was seen at another hospital in the city because of continued high fever, sore throat, and rash. At that time a diagnosis of scarlet fever was made and the child was admitted to the hospital for infectious diseases. The following data were reported at that time: Hgb 8.6 gms, WBC 49,000, Polys 61%, Bands 33%, Lymphocytes 3%, Monocytes 2%, Eosinophils 1%. Blood sugar 82 mgm. %, CO2 23.8 mEg/1. Chest Film: Compatible with pneumonitis. Abdominal films: Enlarged Liver and gas in the transverse colon. Lumbar puncture revealed no cells in the fluid. The following day the WBC was 36,400 with Polys 72%, and Bands 24%, and the serum bilirubin was 8.4 mgm.%. The sickle cell preparation was negative. The child was then transferred on the sixth day of his illness to the Henry Ford Hospital with the diagnosis of possible hepatitis or liver abscess.

On admission he was acutely ill, dehydrated, febrile (102°F), and icteric. The eyes, ears, nose, throat and chest were not remarkable. The abdomen was somewhat distended and tympanitic, but soft. The liver was greatly enlarged reaching down to the pelvic brim.

Figure 1

Flat film of abdomen showing mass in right upper quadrant which appears confluent with the liver.

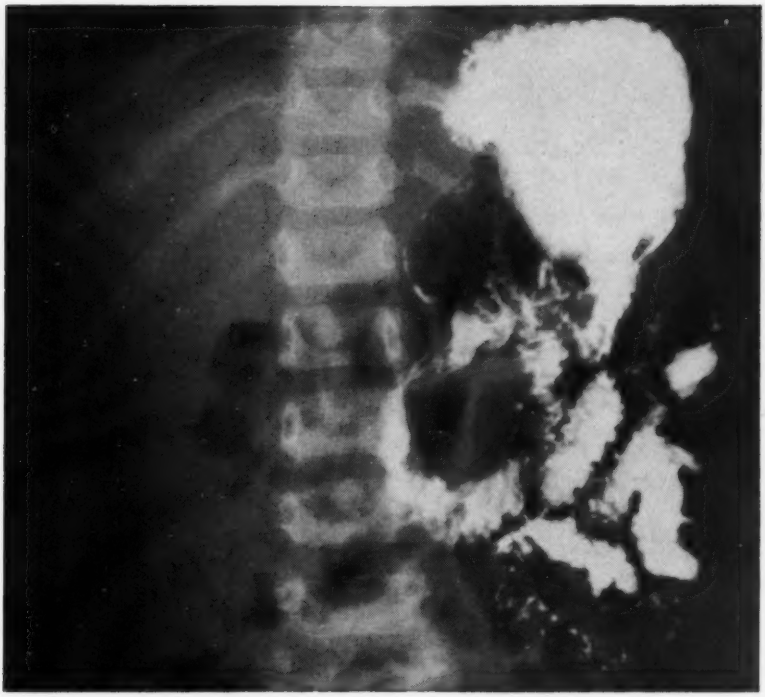

Figure 2

Upper gastrointestinal study showing the duodenal loop displaced to the left of the midline.

He was treated with naso-gastric suction, intravenous fluids, and large doses of penicillin in the infusion fluid. Over the next seven days his fever gradually subsided to near normal. The serum bilirubin fell from Direct 4.48 mg.%, Total 6.36 mg.% to Direct 1.1 mg.%, Total 1.8 mg.%. The leucocytes ranged from 33, 750 on admission to 26,600 on the sixth day, with polymorphonuclear count of 86% to 95%. Liver flocculation tests were normal. Serial blood cultures for bacteria were all negative. Stool culture was negative for pathogenic bacteria. No virus was isolated from the stool collected the day after admission.

Clinically the child improved. However, a mass remained in the right upper abdomen and as the abdominal discomfort improved the mass could be more easily defined. It appeared to be part of the liver. X-ray studies (figures 1 and 2) showed the mass to displace the lower pole of the right kidney laterally, the hepatic flexure of the colon downward, and the duodenum to the left of the midline. The diagnosis of a mass in the area of the porta hepatis was considered most likely. Our first consideration was liver abscess, and the second was tumor.

On the seventh day after admission laporotomy was performed and the mass was found to be a very large thin walled gall bladder filled with "white bile" (figure 3). There were no stones in the gallbladder. The cystic duct appeared obliterated, and the

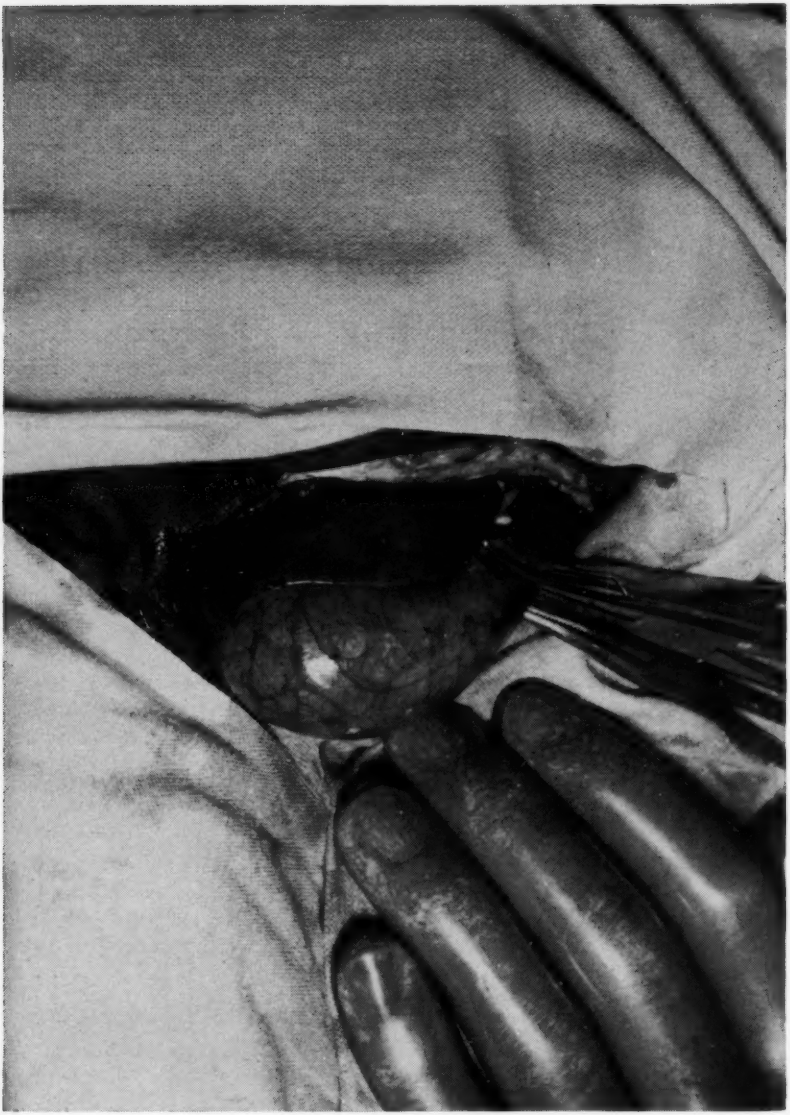

Figure 3

The large distended hydropic gallbladder. The liver appears normal.

structures in the porta hepatis were injected and thickened with moderate edema. The gallbladder, however, was not thickened but was moderately injected. After aspiration of the material within the gallbladder, the structure was removed without

difficulty. Cultures of the aspirate as well as of peritoneal fluid were all negative for bacterial growth. The pathology report on the tissue removed revealed acute and chronic cholecystitis.

Post operatively the child recovered uneventfully, and he was released from the hospital on the tenth day following surgery. Five months later he is perfectly well and has had no illness during that time that has required the service of a physician.

In summary, this case illustrates how gallbladder disease in children is frequently not considered very prominently in the differential diagnosis. Acute cholecystitis is not common in children and a preceding acute systemic disease, so frequently a forerunner of this problem, may obscure the problem and make correct diagnosis difficult. Its detection, however, is extremely important so that proper treatment may be instituted. The treatment of choice is cholecystectomy. Common duct exploration is not mandatory on the basis of jaundice alone, as jaundice is so infrequently associated with common duct stones in the absence of stones in the gallbladder in childhood.

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VACCINATION AGAINST TUBERCULOSIS WITH ULTRASONIC-VIBRATED TUBERCLE BACILLI

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Numerous attempts have been made by many investigators[1-3] to induce protective immunity against tuberculosis by a variety of vaccination programs. Early studies were initiated shortly after the discovery of the tubercle bacilli by Koch in 1882. Since this time, the majority of experiments have been conducted on the basis of four types of vaccines as follows:

1. Preparations of tubercle bacilli killed by a variety of physical and chemical methods.
2. small numbers of living, virulent tubercle bacilli.
3. species of *Mycobacterium* isolated from nonmammalian sources.
4. avirulent organisms of originally virulent strains which were attenuated by various methods.

Immunization with a variety of living, attenuated strains and with several non-living preparations has been shown to produce a significant degree of enhanced resistance for both domestic and laboratory animals as well as man. However, only one of these has been used to any extent in the latter. This vaccine is prepared from an attenuated bovine culture and is known as BCG (Bacille Calmette-Guérin).

Vaccination with BCG preparations has stimulated numerous controversies during the past four decades. The general desirability of this approach to the tuberculosis problem has been evaluated on the basis of efficacy, safety etc. Millions of people have been vaccinated with BCG vaccines during recent years but there is still no absolute agreement on this subject. As a result, there are persuasive arguments for and against the use of these vaccines in the current journals.

The literaure[4-7] contains numerous reports on the advantages and disadvantages of BCG vaccines. The data on this subject can be summarized as follows:

1. The vaccines give some protection in those individuals who are directly exposed to tuberculosis infection either at home or at work.
2. a reduction of tuberculosis occurs in many of the general populations wherein the individuals have low living standards and high tuberculosis rates.
3. the extent and duration of protection, as well as the contribution to the control of tuberculosis in areas where tuberculosis services are good, should still be regarded as problematical.

Ultrasonic-vibrations were used by Kress[8] in 1948 to kill a suspension of virulent human tubercle bacilli. A few guinea pigs were vaccinated subcutaneously with the killed suspension and challenged six weeks later by the intranasal introduction of

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virulent tubercle bacilli. The animals failed to develop tuberculosis but it should be emphasized that the experiment lacked adequate controls. Therefore, this study cannot be considered to have much significance.

Our objective was to investigate the immunizing properties of ultrasonic-treated tubercle bacilli and to compare these preparations with BCG vaccines. We were especially interested in this approach since chemically and heat-treated whole-cell vaccines have been studied for years with questionable promise. It was decided to use several strains of tubercle bacilli which were both virulent and avirulent for man.

MATERIALS AND METHODS

The vaccines reported in this study were prepared using *Mycobacterium tuberculosis* varieties identified as H37, H37Rv, H37Ra as well as a chromogenic strain of acid-fast bacillus. Suspensions of each organism were vibrated separately at 10,000 oscillations* per minute for periods of 5-15 minutes. Since viable organisms were found in all treated preparations it was decided to treat all preparations with 0.35 per cent tricresol in order to inactivate the small number of living tubercle bacilli and have it act as a preservative at the same time. Multiple subcultures for sterility testing were examined for 150 days because it has been our experience that 80-120 days was not sufficient. A total of eleven vaccines (see Table I) were prepared using the above methods in an attempt to obtain preparations which might be effective immunizing agents.

Table I

ULTRASONIC TREATMENT OF TUBERCLE BACILLI

Vaccine #	Organism	Ultrasonic Vibrations in Minutes	mg of Nitrogen per 100 ml of specimen
1	H37Rv	5	1108
2	H37Rv	10	1198
3	H37Rv	10	1007
4	H37Rv	15	1108
5	H37Rv	15 *supernatant	33
6	H37	5	780
7	H37	10	697
8	H37	15	617
9	H37	15 *supernatant	32.8
10	H37Ra	15	71.8
11	Chromogen	15	61.5

*The supernatant of each of the 15 minute treated H37Rv (#5) and H37 (#9) were also tested for their immunizing properties.

This report deals with two series of experiments. The first consisted of an evaluation of the evelen vaccines using a group of 10 guinea pigs for each preparation. The second series consisted of two ultrasonic-treated antigens as well as BCG. Guinea pigs weighing

*A sonic oscillator, manufactured by Raytheon Manufacturing Company, Waltham, Mass., was used.

approximately 300 grams were used throughout these studies. For randomization, the cages in any one experimental group were distributed so that one cage would be found in the first quarter of the total number, a second cage in the second quarter of the total and so on. Tuberculin sensitivity testing of control and vaccinated animals was conducted using Eli Lily's tuberculin preparation. The tuberculin tests were performed 28-30 days after the initial vaccination procedure together with tests of the unvaccinated controls. The results were read at 24 and 48 hours, a positive reaction being 5 mm. or more in minimum diameter. In some instances, reactions were strong with a blanched, later necrotic, center.

The immunization doses were administered subcutaneously in the inguinal region. Each animal received five injections at 7 day intervals with the following volumes: 0.5, 1.0, 1.5, 2.0 and 2.0 mls. A comparable group of animals recieved corresponding volumes of saline. A supply of freeze-dried vaccine was obtained from Sol Rosenthal of the Research Foundation, Chicago. It was administered by the "Multiple Puncture Disc Technique" as outlined in the directions of the supplier. Three weeks after the last immunizing dose the animals were challenged with 1 ml. of a virulent strain of *Mycobacterium tuberculosis* var. *hominis* (approximately 0.1 mg., semi-dry weight, of a ten day culture) subcutaneously in the inguinal area.

The experiments were evaluated in two ways: (1) the extent of gross and histological tuberculous infection (Table 2, 3) as measured by an adaptation of the Feldman Index[9]. Observations were as detailed as possible on all major organs — lungs, liver, spleen, inguinal and retroperitoneal nodes. Acid-fast smears and cultures were also performed on the specimens. (2) by the average survival time for each group of animals.

Table II*

Key Table for Evaluating *Histologically* the Extent and Character of the Tuberculous Lesions in Experimentally Infected Guinea Pigs. Assign the Highest Number Corresponding to the Description of the Lesion in Each Tissue.

Extent and Character of Lesions in Section Examined	Spleen	Lung	Liver	Site of Inoculation and Contiguous Lymph Nodes	If Lung is Negative Examine Tracheo-bronchial Lymph Nodes
Progressive lesions present					
Extensive involvement	35	30	25	10	10
Moderate	20	20	20	10	10
Slight	10	10	10	10	10
Nonprogressive lesions only					
Fibrosis, hard tubercles	3	3	2	1	1
Fibrosis or calcification only	1	1	1	1	1
Maximal values = 100 total	35	30	25	10	10 (If lung is negative)
If only inactive lesions, maximal values less than 10	3	3	2	1	1 (If lung is negative)

*This table was copied from Feldman's paper (9).

Table III

Method for Evaluating by *Gross Appearance* the Extent and Character of Tuberculous Lesions in Experimentally Infected Guinea Pigs*.

Extent of Involvement in Tissues Examined	Spleen	Lung	Liver	Site of Inoculation	Tracheal bronchial Nodes with Negative Lung
Extensive 3+ to 4+	35	30	25	10	10
Moderate 2+	20	20	20	10	10
Slight 1+	10	10	10	10	10
Maximum Values 100 Total	35	30	25	10	10 (If lung is negative)

*Slight Modification of Feldman's procedure[9].

Result: The purpose of the first series of experiments was to ascertain whether there was any evidence that the ultrasonic-treated organisms possessed potential antigenic value. The animals in the eleven experimental and one control group — No. 12 — (Table 4) were autopsied at the time of death and the average survival rates are summarized in Table 4. The data show that antigens #7 and #8 increased the survival time to a greater extent than the other antigens. Statistical evaluation of the results obtained on the animals in each group showed that the probabiliy values for vaccine #7 and #8 were significant.

Table IV

Identification of Vaccines

	H37Rv				H37					H37Ra	Chromo-genic	Control
	1	2	3	4	5	6	7	8	9	10	11	12
Average number of days after challenging	68	69	62	81	36	85	128	108	40	86	77	48

The apparent increase in resistance to tuberculosis produced by antigens #7 and #8 in the first series of experiments led us to compare their immunizing properties with those of BCG as well as to confirm the results of the first series of experiments. Thirty animals were used in each group of the second experimental series including a similar number in two controls (one of which received saline and the other no injections). The guinea pigs were tested with tuberculin after the 5 immunization doses had been given at weekly intervals. Slightly more than fifty per cent of the animals showed strongly positive tuberculin tests. The other fifty per cent were either weekly reactive or negative.

The results of the survival times for the animals of the second experimental series are listed in Table 5. The data serve to emphasize that BCG produced much greater resistance against tuberculosis than did vaccine preparations #7 and #8. Thus, there is a striking degree of protection (Table 5) exhibited by BCG vaccine. This preparation produced a survival time of greater than 107 days as compared to the 41, 39, 51 days for vaccines #7, 8 and the saline controls respectively. The control group which did not receive a challenge dose (Table 5) was included to evaluate intercurrent infections in the animal colony. The animals which survived in this

latter group were sacrificed 200 days after the date of challenge and showed an average survival value of greater than 161 days.

Table V

Results of Experimental Series #2

Vaccine	Description	Per cent of animals Tuberculin Positive after Immunization	Average Survival Period in Days
#7	H37 10 min.	55%	41
#8	H37 15 min.	66%	39
BCG	Research Foundation	59%	>107
Controls	Saline —Animals challenged	0%	51
Controls	—Saline only —No challenging dose	0%	>161

All animals which had received a challenging dose and survived for a two week period thus avoiding intercurrent infection, eventually showed moderate to extensive tuberculosis. This conclusion has been based on the results obtained with the Feldman method[9] for evaluating both the gross and histological tuberculosis (Tables 2 and 3) changes in the infected guinea pigs.

Intercurrent infections were usually high in all groups. Therefore, it was always necessary to quarantine the animals for several weeks before beginning the immunizing dose. To avoid errors due to intercurrent disease it was imperative that all animals be autopsied rather than to depend on death and survival rates only.

DISCUSSION

The results of the first experimental series provides further evidence (Table 4) that a degree of enhanced resistance to tuberculosis can be produced not only by living but also by killed tubercle bacilli. Electron micrographs of the ultrasonic treated suspensions showed both intact and fragmented cells. Vaccines number 5 and 9 which consisted of supernatant from H37 preparations were immunogenically inactive. Thus, one may conclude that the sediments were capable of enhancing resistance to tuberculosis to a greater extent than the supernatant materials under test.

An important but controversial issue in tuberculosis is the role of tuberculin skin hypersensitivity in protective immunity. The experiments in which the vaccines were capable of increasing the resistance of the animals to tuberculosis often did so without making the animals skin-hypersensitive to tuberculin. The reverse was also common — the tuberculin positive animals frequently showed little or no resistance to the challenging dose of tubercle bacilli. Emphasis should be placed on the fact that the absence of skin hypersensitivity to an antigen does not always indicate total absence of systemic hypersensitivity. Furthermore, tuberculin preparations which were employed to test for sensitivity consisted of the usual heated preparations, and the absence of a reaction to these does not necessarily mean that the animal would not be sensitive to unheated tuberculoproteins. Thus, the independence of tuberculin skin hypersensitivity and acquired resistance to tuberculosis should be considered in discussing this complex subject.

The work of Weiss[3] as well as this report support the contentions of other investigators that the development of acquired immunity to tuberculosis does not require infection with living tubercle bacilli. Immunity to tuberculosis can be bestowed by either components or whole nonliving cells which at times may also lack skin-sensitizing properties.

An attempt was made with the first series of our experiments to determine the extent of antigenic activity of the eleven vaccines. Having demonstrated that vaccines # 7 and 8 were statistically significant when compared with the controls, the second series was designed to answer two questions:

1. Would the vaccines retain their antigenic activity on storage for a one year period?
2. How effective would the preparations be when compared with BCG?

A comparison of the survival periods (Table 6) shows vaccines #7 and 8 to be of extremely short durations. In fact, the figures are smaller than those shown for the control group. This might indicate that toxic substances as well as other unknown factors may have contributed to a shortening of the survival time. The wide differences between the results of the first and second series may possibly be due to loss of potency during the storage period.

If one examines the survival period for the BCG group (107 days) in series number 2 (Table 6) and compares this with the results of series number 1 (128 and 108 days), the data show that the nonliving vaccines were at least as effective against tuberculosis as the living one (BCG). It is evident from a perusal of the literature that the majority of experimental data in which nonliving antituberculosis vaccines (ie. phenol killed, methanol extracts etc.) were tested that such preparations possess approximately equal immunogenicity as living, attenuated ones. Although a number of technical problems — variation in dosage, route of administration, vaccination-challenge interval, method of evaluating the data, etc. — require further attention. There is sufficient evidence that killed tubercle bacilli and some of their extracts definitely have immunizing properties[12].

Table VI

Survival Period in Days for the Two Series of Experiments

	Series 1	Series 2
Vaccine #7	128	41
Vaccine #8	108	39
Control	48	51
Saline + Challenging dose		
BCG	not done	107

Safety of vaccination is another very important consideration since one wants to prevent, not initiate progressive disease. It should be understood that safety, as it refers to any pathologic process due to vaccination, is not always assumed. Therefore,

it is of primary importance that the toxigenic properties of nonliving vaccines be investigated.

It is possible that there may be a decrease in efficacy with corresponding increases in dosages[13] even to levels still below that at which physical symptoms of illness appear. This is an indication that a threshold area of toxicogenicity exists in evaluating "tuberculosis vaccines".

Other arguments in favour of killed vaccines have been previously reviewed at length by Weiss[12]. The results of the first experiment in this report are an indication that ultrasonic-treated bacilli have immunizing properties. The increase in resistance demonstrated by the prolonged survival time of the animals suggests that further studies be done. Furthermore, the data obtained in the second experiment show BCG to be a superior vaccine. One cannot discount the fact that vaccines #7 and 8 showed comparable effectiveness in experimental series number one.

SUMMARY AND CONCLUSION

Two of eleven vaccines prepared by ultrasonic vibration of four strains of *Mycobacterium* were found to stimulate increased resistance to tuberculosis when compared to the saline control group which was challenged with comparable inoculum. The data were statistically significant .The other nine preparations did not show protective activity to the same extent.

The two vaccines were not as effective after storing at 4°C for a one year period. In fact the 'stored' vaccines appeared to cause a toxic effect. Parallel experiments showed that BCG prolonged the survival time to a much greater degree than the two 'stored' vaccines.

A review of the data suggests that the ultrasonic-treated antigens (vaccine #7, 8) in the first series of experiments were equally as potent as BCG in the second series. For this reason as well as the fact that the results of the first experimental series were statistically significant, further studies should be undertaken using freshly prepared ultrasonic treated vaccines and BCG.

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WARTHIN'S TUMOR OF THE PAROTID GLAND

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Warthin's tumor of the parotid gland (papillary cystadenoma lymphomatosum) is a rare, benign tumor occurring usually in or adjacent to the parotid salivary gland. Although this lesion was emphasized by Warthin in 1927 when he published a report of two cases,[1] and coined the term papillary cystadenoma lymphomatosum, he recognized the fact that this lesion had been first described as a definite pathological entity by Albrecht and Arzt in a paper published in 1910 entitled "Papillary Cystadenoma in a Typical Lymph Node".[2] Martin and Ehrlich, in 1944, were the first to employ the term Warthin's Tumor.[3]

Our interest in this tumor was stimulated by an unusual case with bilateral parotid involvement and pathological evidence of multicentric origin. Another unique feature was the fact that there had been two recurrences of the lesion following surgical removal. The following is a report of our experience with this patient and a review of the Warthin's tumors of the parotid gland seen at the Henry Ford Hospital from 1920 to 1960.

CASE REPORT

In August 1957, a 50 year old white male presented himself to the surgery clinic of the Henry Ford Hospital with the chief complaint of a small lump at the angle of his left jaw just below the ear. He first noticed this growth six years previously in 1951 when it began to increase in size. There was no pain, tenderness or drainage. In 1953, two years after the initial onset, he was seen by a physician and the tumor was excised. One month following this operation he noticed another asymptomatic growth at the same site. This lesion was the size of a marble and did not enlarge. In 1954, one year after the initial surgery, the mass was again excised. He was informed that both of these extirpated tumors were benign. Three weeks following his second operation he noticed another small growth in the same region as the two previous operative sites. There had been no symptoms associated with this lesion other than a progressive enlargement when he was seen by us in 1957.

At that time physical examination revealed a healthy appearing white male with a freely movable nodular mass 3 x 3 centimeters in size located in the left upper cervical region just beyond the angle of the jaw. The mass was firm, non-tender and free from the overlying skin. The lesion appeared to be associated with the parotid gland and a tentative diagnosis of recurrent mixed parotid tumor was made. No abnormalities of the nasopharynx were found and there was no associated cervical lymphadenopathy.

A pathology report of the previously excised lesions was obtained and revealed them to be typical of papillary cystadenoma lymphomatosum. With this encouraging evidence of a benign tumor, a left total parotidectomy with preservation of the facial

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nerve was performed by one of the authors (R. F. S.). The patient made an uneventful recovery. The pathological diagnosis was papillary cystadenoma lymphomatosum with evidence of multicentric origin. Typical epithelial and lymphoid elements were seen both in the main encapsulated nodule and also in a separate focus in the surrounding parotid tissue.

One year later, in October 1958, the patient presented himself with another asymptomatic lump the size of an acorn but this time on the opposite side just below and behind the right ear. It had been present for eight months but had not concerned him unduly until the last three months when the lesion began to increase in size more rapidly. Examination at this time revealed a non-tender mass measuring 3 x 4 centimeters behind the right ear and extending to the angle of the jaw. The mass was circumscribed and did not seem to be fixed to the overlying skin. The scar of the left parotidectomy was well healed without evidence of recurrent tumor. The patient declined surgical removal and elected to have the lesion closely observed.

In August 1959, because of progressive increase in the size of the tumor, he was admitted for definitive treatment. By this time the mass had increased to the size of a plum. A right total parotidectomy was performed (R. F. S.). The pathological examination again revealed a papillary cystadenoma lymphomatosum with multicentric origin. Grossly, there were two distinct nodules which showed a typical pattern when examined microscopically. In addition, two adjacent lymph nodes contained separate foci of the tumor. Recovery was uncomplicated. Until now there has been no evidence of recurrence of the tumors on either side.

Comment: This case held considerable interest for us because of the bilateral involvement (the only one in our series) and also the rather unusual fact that the tumor had recurred on two occasions following local surgical excision and therefore required a more extensive parotidectomy. Pathologically it was also striking in that there was bilateral evidence of multicentric origin. To have all of these unusual features combined in one case is indeed rare.

DISCUSSION

Warthin's tumors are not common. Two hundred and nine parotid tumors have been indexed at the Henry Ford Hospital from 1920 to 1960. As can be seen in

Table I
PAROTID TUMORS
Henry Ford Hospital — 1920-1959

Pathological Type	Number	Percent
Mixed Tumor	144	69
Carcinoma	35	16.5
Warthin's Tumor	19	9
Lipoma	4	2
Reticulum Cell Sarcoma	2	1
Hemangioma	2	1
Neoplastic Cyst	2	1
Myoepithelial Tumor	1	0.5
	209	

Table I, by far the most frequent pathological type encountered was the typical mixed parotid tumor. Following parotid carcinoma were the nineteen Warthin's tumors represented nine per cent of the total.

These nineteen tumors have all been reviewed microscopically and each was found to be a typical papillary cystadenoma lymphomatosum. Their pathological characteristics will subsequently be discussed in detail.

A study of the case histories in this group revealed the patients to range in age from 25 to 69 years with the average at 54 years. There were fifteen males and only four females which is representative of the sex distribution. The time that the tumors were known to be present varied from one month to twelve years. The average duration of a noticeable parotid mass prior to surgical removal was 35 months. The size of the tumors ranged from one centimeter to six centimeters and correlated well with their duration; namely, the largest tumor was present for the longest period of time. Most of the tumors grew slowly; however, there were some that apparently remained dormant for two to three years before undergoing within a few months a period of relatively rapid enlargement. Fourteen of the tumors were located in the superficial lobe of the parotid gland, two in both the deep and superficial lobe, and three in lymph nodes outside of the parotid gland proper but adjacent to it. In only one case was there bilateral parotid involvement. These clinical features correlate well with a series of Warthin's tumors compiled by Foote and Frazell.[4]

In Table II we have listed chronologically the nineteen Warthin's tumors in our series. It should be pointed out that the recent increase in frequency of this tumor probably does not reflect a true increased incidence but rather reflects our considerably greater clinical and operative experience at the Henry Ford Hospital during the past five to ten years. Also it is reasonable to assume that pathological identification of this tumor has been more precise during the past decade.

Table II

WARTHIN'S TUMORS

Henry Ford Hospital — 1920-1960

Year	Sex	Age	Size (cm.)	Duration (mos.)	Recurrence
1938	F	46	4	18	
1940	M	55	2	24	
1946	M	55	3	12	
1947	M	61	3	12	1
1949	F	25	2	6	
1950	M	45	3	24	
1953	M	33	2	4	
1953	M	55	1	1	
1955	M	55	3	60	
1956	F	67	2	4	
1957	M	63	2	2	
1957	M	46	3	3	
1957	M	66	6	144	
*1957	M	54	3	72	2
1959	M	69	4	5	
1959	M	67	3	2	
1959	F	58	3	2	
1959	M	50	4	60	
*1959	M	56	3	12	

*Reported case with bilateral involvement.

The clinical characteristics of Warthin's tumors are such that they cannot be easily distinguished from other parotid tumors. Typically, they are painless, non-tender and non-exudative lesions which commonly present at the angle of the jaw and seldom become larger than five centimeters in size. They are firm to palpation and may be fixed to underlying structures but are usually not attached to the overlying skin.

Papillary cystadenoma lymphomatosum ordinarily is diagnosed prior to surgery as a mixed parotid tumor. It also may be erroneously diagnosed as a branchial cleft cyst when the mass is fluctuant and lies below the parotid gland. A diagnosis of a tumor of lymphoid origin or a lymphadenitis may be made preoperatively when the lesion presents at a more distant location from the salivary gland.[4,5] In only one of our cases was the correct diagnosis of Warthin's tumor made prior to surgery. Nine of our nineteen tumors were diagnosed preoperatively as mixed tumors of the parotid, three cases were diagnosed as branchial cleft cysts, two cases as carotid body tumor, two cases as cysts of the parotid gland, and two cases as lymphadenopathy.

The customary management of papillary cystadenoma lymphomatosum has been local surgical excision. Irradiation is generally not indicated. As shown by our nineteen cases a limited surgical approach is usually quite satisfactory as there were only three instances of recurrence (Table 2). Local excision, however, will be inadequate if the tumor is multicentric. This is illustrated by the two previous recurrences in our reported case. It would seem, therefore, that consideration should be given to performing a more extensive type of parotidectomy as the initial form of surgical therapy. Certainly if a secondary operation should become necessary it will be technically more difficult and the hazard of facial nerve injury is considerably greater.

PATHOGENESIS

There has been considerable discussion concerning the origin of the papillary cystadenoma lymphomatosum. Originally Albrecht and Arzt thought that the tumor they described developed from heterotopic salivary gland tissue found in lymph nodes in the region of the parotid gland.[2] Warthin believed this tumor to be derived from an anlage of the eustachian tube because of the similarity of the mucosal structure and the intimate relationship between the epithelium and lymphoid tissue, characteristic of pharyngeal mucous membranes in general.[1] Some writers have expressed the belief that the papillary cystadenoma lymphomatosum arises primarily from salivary gland tissue and that the lymphoid constituent is only secondary.[6] Other investigators have maintained that the tumor arises from the ectoderm of branchial clefts in which the lymphoid and epithelial elements are likewise closely associated.[7]

Thompson and Bryant reported an excellent study where they made serial sections of the head and neck region of eighteen embryos in order to visualize the development of the salivary glands.[8] They also compared 100 normal parotid and 50 normal submaxillary glands histologically with 50 branchogenic cysts and fistulas, and 23 examples of papillary cystadenoma lymphomatosum. They noted different fundamental features in the submaxillary and parotid glands of the embryos they studied. No lymphoid tissue was found by them in submaxillary tissue, while in parotid glands, lymphoid

tissue and lymph nodes were relatively common. On the basis of this study, they concluded that the papillary cystadenoma lymphomatosum arises from parotid ductal epithelial elements included in lymph nodes and is due to neoplastic proliferation of parotid ductal epithelium with concomitant proliferation of lymphoid tissue. They point out as a further basis for their contention that no examples of Warthin's tumor have been recorded in the literature except from within or near the parotid salivary gland. No unquestionable case of Warthin's tumor arising in a submaxillary gland has been found in the literature. Bernier and Bhaskar have elaborated this study and detailed the points supporting the concept of origin of these tumors from salivary duct epithelium detained in lymphoid tissue within or adjacent to the parotid salivary gland.[9] This is currently the most popular theory and probably represents the correct origin of these tumors.

PATHOLOGY

The nineteen tumors studied in this laboratory were generally described as solid, oval or lobular masses which varied from 1.5 to 4 centimeters in maximum dimensions. A capsule was described in fourteen cases. The majority of tumors were soft and contained cysts of varying size. The color varied from white to red-brown, the majority being tan and resembling lymphoid tissue. The cysts contained yellow turbid fluid or tenacious yellow-white material, frequently described as purulent or caseous. The

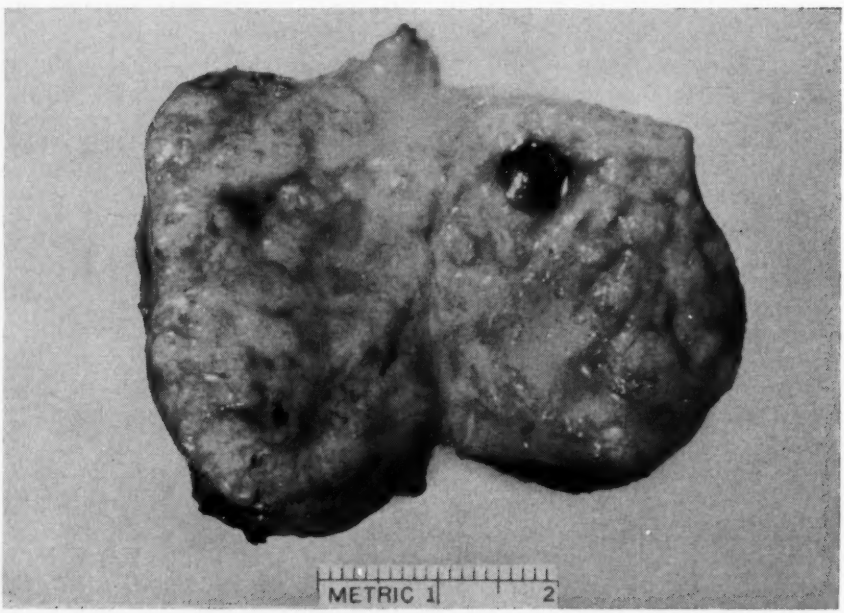

Figure 1

Gross photograph of papillary cystadenoma lymphomatosum showing fairly solid structure. Lobulation is striking.

gross appearance is often diagnostic and in most cases should be recognized at the operating table. There may be some variations depending largely on the number and size of the cysts (Figure 1 and 2).

Figure 2

Gross photograph (after fixation) of encapsulated papillary cystadenoma lymphomatosum lying within parotid salivary gland. The intracystic papillary growth is evident.

The histologic appearance of papillary cystadenoma lymphomatosum is also quite characteristic. Cystic spaces are lined by a high columnar eosinophilic epithelium with prominent uniform nuclei. These nuclei have a tendency to palisade toward the lumen of the cyst. Underlying this are varying amounts of stroma containing lymphoid tissue, often with prominent reaction centers (Figure 3). The lumina of the cystic spaces generally contain an eosinophilic granular material and variable numbers of inflammatory cells and cellular debris.

Acicular clefts are noted not infrequently. Occasional goblet cells are present, which are muci-carmine and PAS positive. Epidermoid metaplasia is infrequently encountered, but does appear. Focal areas, in which the epithelial component predominates with little lymphoid tissue, are seen. A thin capsule was demonstrable in seven instances in this series. There was invagination of the parotid gland and fat into the tumor mass in one case (Figure 4). The capsules include what appear to be

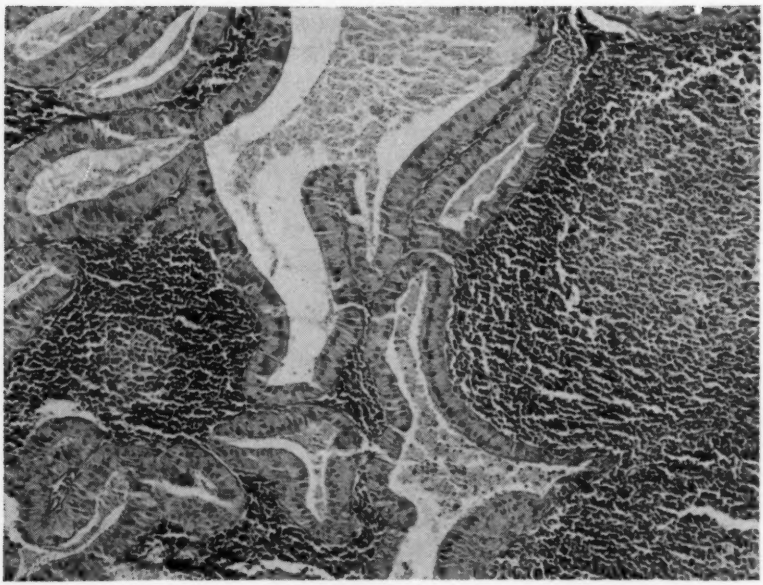

Figure 3

Papillary cystadenoma lymphomatosum showing columnar epithelium lining the cystic spaces and lymphoid tissue with reaction centers in the stroma. X115.

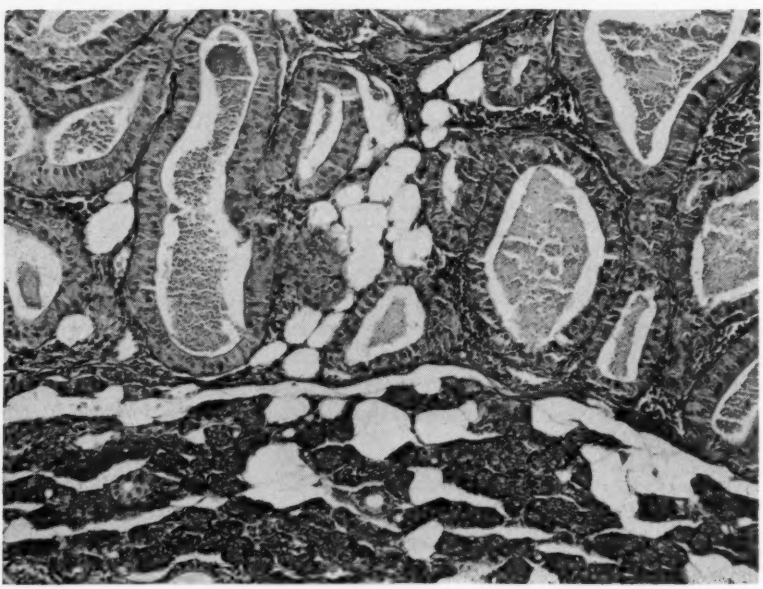

Figure 4

Invagination of salivary gland and adipose tissue into papillary cystadenoma lymphomatosum. X115.

lymphatics and in four instances an area containing a duct, blood vessel, and nerve, in close relationship, suggested a hilus. Prominent sub-epithelial fibrosis was seen in five tumors.

Two tumors in our series bore certain similarities to the cystic mucoepidermoid tumor of "favorable" prognosis, adding a further example of the overlap of certain patterns with those of other salivary gland tumors.[9]

Ducts of parotid salivary gland type were found in adjacent lymphoid tissue in six of the nine cases in which adequate tissue was available for study (Figure 5). One tumor, characterized clinically by multiple recurrences, was multicentric and in another case, the uninvolved salivary gland contained unencapsulated foci suggestive of incipient tumors of the same type. Two tumors were associated with sialadenitis and one with an adjacent, but distinct oxyphil adenoma.

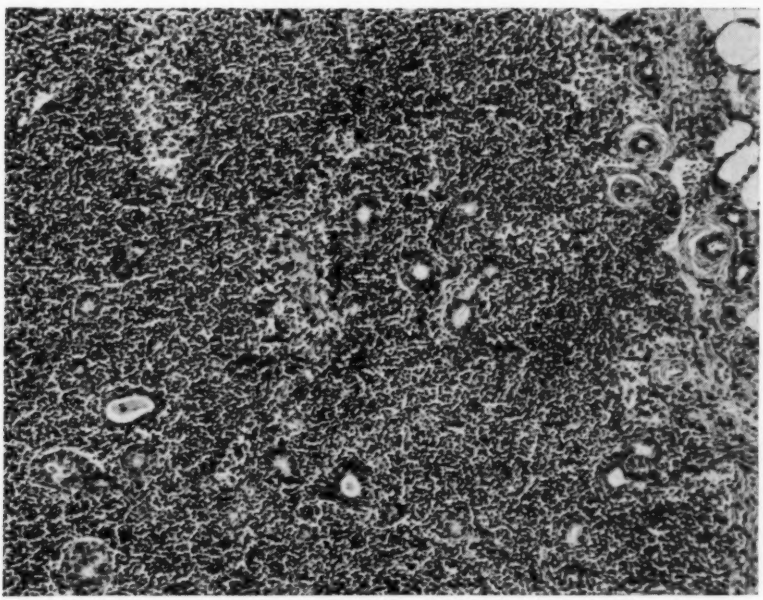

Figure 5

Ducts of salivary gland type in a lymph node adjacent to a papillary cystadenoma lymphomatosum. X115

SUMMARY AND CONCLUSIONS

Our experience with nineteen cases of Warthin's tumor of the parotid salivary gland is reviewed together with a report of one case with two recurrences and bilateral involvement.

Papillary cystadenoma lymphomatosum is grossly, as well as microscopically characteristic, and should in most cases be recognized at the time of surgery. The

features which are most helpful in differentiating it from other lesions of the parotid gland are the tan lymphoid appearance and the unusual cystic spaces containing turbid material.

The bulk of evidence indicates the origin of these tumors to be from parotid duct epithelial inclusions within lymphoid tissue in the region of the parotid gland and adjacent soft tissue.

Because papillary cystadenoma lymphomatosum may be multicentric, and therefore recurrence possible, it is suggested that consideration be given to total parotidectomy as the primary form of surgical treatment.

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THE TRENDELENBURG OPERATION: PULMONARY ARTERY EMBOLECTOMY

THOMAS GAHAGAN, M.D.*

In reading the discussion of Neuhof's paper on pulmonary embolectomy presented at the 1944 meeting of the American Surgical Association[1], it is easy to detect a lack of enthusiasm for the operation, and a dim outlook as to its future. There was good reason for this at the time, in addition to the lack of success which the procedure had met in this country. The use of methods for the detection of post operative phlebothrombosis such as the Homan's sign had become widely disseminated. The introduction of femoral vein ligation proximal to the thrombus, early ambulation, and to a lesser extent prophylactic bandaging of the legs gave reason to think that with the proper vigilance, emboli could be prevented from entering the pulmonary artery, or thrombosis in the leg veins minimized. The introduction of heparin therapy by Murray and Best in Toronto[2] and its first use in this country by McClure and Lam[3] gave further hope that prevention of pulmonary emboli was an attainable goal. In reveiwing statistical surveys it is difficult from our vantage point now to assess accurately the impact which these measures have had on the incidence of serious sequelae of leg vein thrombosis in the postoperative period. One thing is certain, however, the problem of fatal pulmonary embolism is still with us. Each year a large surgical service will have to deal with a number of massive embolizations to the pulmonary artery[4]. For this reason surgical thinking in this institution and elsewhere has come back to the consideration of pulmonary embolectomy.

Recently this operation, proposed by Trendelenburg in 1908[5], was carried out in this hospital for the first time. Although a massive clot was removed from the main pulmonary trunk and from the right and left main branches, the patient succumbed with residual thrombus in the distal pulmonary arterial tree.

F. S., a 42 year old man, reentered the hospital on 5/25/60 for the treatment of severe ulcerative colitis .He had had recurring attacks of diarrhea with bleeding which were refractory to medical management. Upon admission he was in an acute exacerbation of his illness. He had continuous bloody diarrhea, abdominal distention, and had lost 20 pounds during the preceding three weeks.

The patient was operated on by Dr. John Wylie on 6/3/60. A one stage subtotal colectomy was carried out and an ileostomy was constructed. The patient's postoperative course was initially characterized by improvement with a functioning ileostomy and good fluid and electrolyte balance. His progress was uneventful until the seventh postoperative night. At about 10 P.M., following a walk in the corridor, he was forced to take to his bed because of a sudden feeling of being unable to breathe combined with a sensation of tightness in the anterior chest. When closely questioned at this time the patient thought that there was a peculiar sensation in his left leg, but denied any pain or tenderness in that location. There was no increase in the diameter of the leg and Homan's sign was absent. The patient presented the picture of a disaster stricken man. His pulse rate was between 140 and 160 per minute. His respirations

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were rapid. His blood pressure was 70 systolic. He was covered with a film of cold perspiration. No murmurs were heard over the precordium and no unusual quality of the cardiac sounds was noted. No rales were audible in the lung fields. The abdomen, aside from the changes relative to the recent operation, was negative.

The impression of the examiners was that the patient had sustained an acute massive pulmonary embolization. Treatment of an emergent nature for this condition was instituted with administration of oxygen by nasal catheter, and the injection of morphine and levophed. An electrocardiogram taken at this time demonstrated incomplete right bundle branch block.

After a period of observation the patient was transported to the operating room in his bed. The patient was placed on a cooling blanket and the skin of the chest was prepared prior to the introduction of an endotracheal tube. Following induction of anesthesia a midline sternal incision was made which was carried down through the sternum with the Lebsche knife. The pericardium was also opened longitudinally. The heart was beating regularly although feebly. The right ventricle in particular was dilated, lending support to the diagnosis of acute obstruction of its outflow, although palpation of the main trunk of the pulmonary artery did not demonstrate a thrombus in its lumen. It was thought worthwhile at this point to gain control of the venous inflow to the right atrium preparatory to opening the pulmonary artery, as is done in the current operation

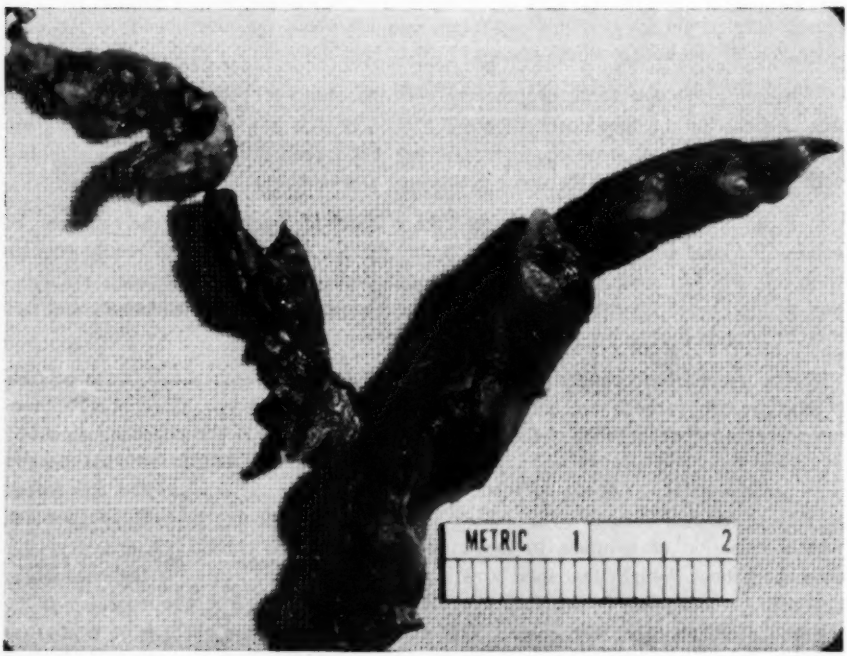

Figure 1
Emboli removed from the pulmonary trunk and the right and left main branches.

of normothermic pulmonary valvotomy. Snares were placed around the superior and inferior venae cavae. The main pulmonary trunk was then dissected away from the root of the aorta and a cotton tape placed around it. Traction sutures were placed on either side of the proposed arteriotomy site. The venae cavae were temporarily occluded prior to opening the pulmonary artery. This maneuver was repeated with each subsequent exploration of the interior of the pulmonary artery. A metal suction tip was inserted into the main pulmonary trunk and directed into the right branch and, on withdrawing it, fragments of thrombus were removed. This was repeated a second time, directing the instrument to the left, and another sizable thrombus was recovered (Figure 1). On a total of three subsequent occasions the metal suction tip and hard rubber catheters were inserted deep into the right and left branches of the pulmonary artery, but no further clot was obtained. Each period of caval occlusion lasted from one to two minutes. Upon opening the caval snares at the conclusion of each period the pulmonary artery opening was closed with a curved Potts clamp. The heart action, which remained regular throughout, become more vigorous following the extraction of the thrombus. However, it subsequently became weaker and the right ventricular dilatation noted at the outset became more pronounced, and did not respond to the injection of epinephrine, calcium chloride and cedalanid more than temporarly. After a prolonged period of resuscitative efforts the heart remained unable to maintain an effective beat and the operation was finally terminated.

Post mortem examination showed the main pulmonary trunk and the initial portions of the right and left main branches to be free of thrombus. Distal to these areas, however, there was organized thrombus extending far down into the pulmonary arterial tree on both the right and left.

DISCUSSION

A median sternotomy was used instead of the T shaped incision with resection of portions of the third and fourth ribs proposed by Trendelenburg. The swift opening of the midline of the ternum achieved by the Lebsche knife, offering excellent exposure of the outflow tract of the right ventricle and the pulmonary artery, has much to recommend it and is the incision we would employ again. It has additional advantages in allowing manipulation of the ventricles in resuscitative maneuvers. Access to the cavae is also good. However, at a future operation we would omit placement of snares around the cavae to control the venous inflow to the heart as an unnecessary step. The right heart is already obstructed and simple clamping of the artery at about the level of the valve would be sufficient to keep right ventricular blood from the field during the short periods of opening the vessel.

With an adequate incision in the main pulmonary trunk large clots were removed from the main trunk and from the right and left main branches. When the arteriotomy was closed with a clamp and the heart allowed to empty itself, the gross right centricular dilatation persisted. Because of the time during which the obstruction had been in effect, it was thought possible that the right ventricle had dilated and stretched so that it was not capable of initiating a forceful contraction after removal of the clot. In fact, however, its outflow was still obstructed, not at its origin, but in the distal portions of the pulmonary arterial tree. Thus the use of cardiac muscle stimulants

was not effectual in restoring a purposeful emptying contraction in the right ventricle. Just how long the right ventricle can be completely obstructed and yet able to resume a competent pumping action is not clear, but it would seem, on the basis of this instance, that residual right ventricular dilatation probably means residual thrombus in the pulmonary artery distal to that already removed.

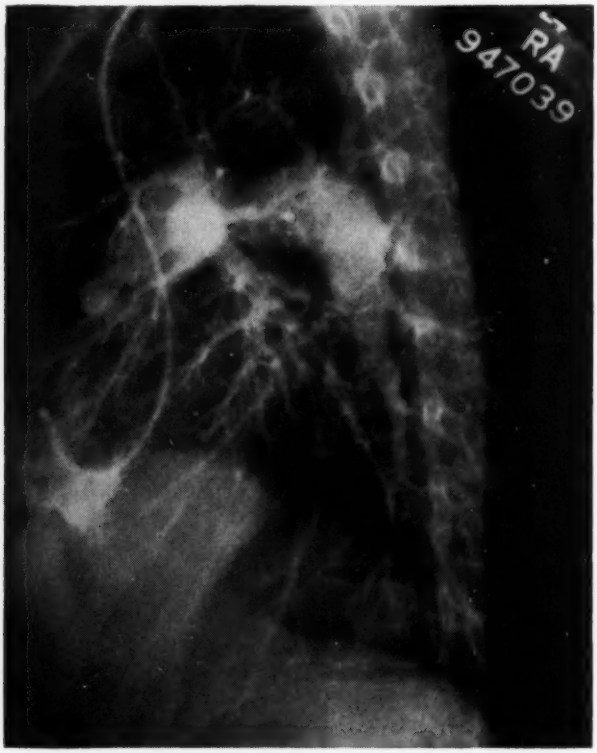

Figure 2

Right heart angiogram lateral projection showing posterior angulation of main pulmonary trunk and right and left pulmonary arteries.

Neuhof and also Beck proposed performing the embolectomy via the right ventricular outflow tract rather than through the pulmonary artery itself as stipulated by Trendelenberg. Mistakes of orientation were cited in which the surgeon opened into the aorta rather than the pulmonary artery[1]. In view of the status of familiarity of surgeons with structures in juxtaposition to the heart at that time this suggestion was undoubtedly a reasonable one. At present, when this region is a commonplace operating site of the thoracic surgeon, the direct approach through the pulmonary artery seems most advantageous. The instruments stipulated by Trendelenburg for use in this procedure were: 1. A rubber tube tourniquet for insertion through the transverse sinus for elevating the great vessels. 2. A hooked sound designed for retrieving the end of the rubber tube, 3. Forceps for dilating the arterial opening, 4. Clot removing forceps, 5. A

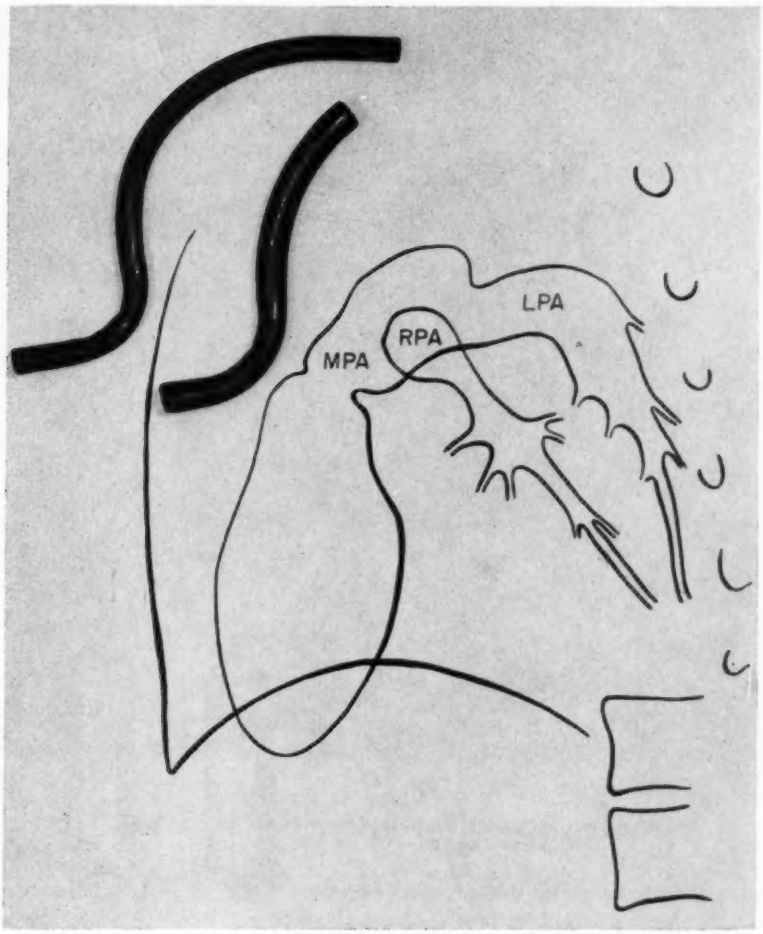

Figure 3

Metal suction cannulas photographed against a 1:1 outline drawing of lateral pulmonary angiogram.

flat bladed clamp for closing the opening in the pulmonary artery. Some of these instruments are obsolete because of the progress in cardiovascular instrumentation. For example, the Potts clamps can be used in preference to a flat bladed clamp. Others seem unnecessary such as the tourniquet for occluding and elevating the great vessels via the transverse sinus, and forceps for holding apart the incision in the pulmonary artery. What would be more useful are catheter tips and extracting tools for manipulation of thrombus in the distal portions of the pulmonary artery. The orientation of the pulmonary artery is unlike that of an artery in a limb, deviating from a straight line by angulation in two planes. In the case reported by Neuhof, as in our case, the insertion of rubber catheters into the pulmonary artery did not succeed in extracting the

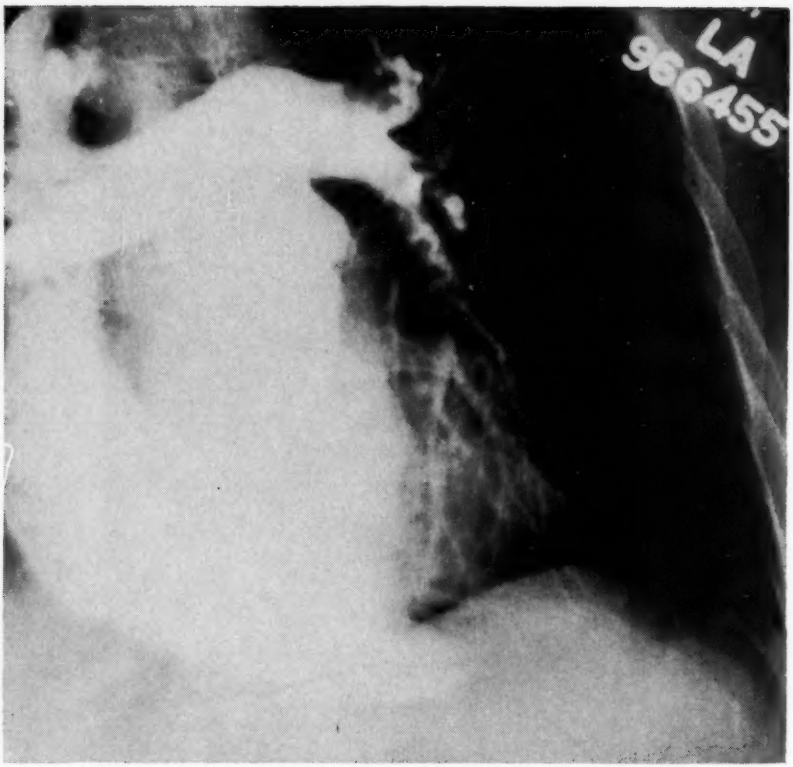

Figure 4
Right heart angiogram, posteroanterior projection showing lateral and inferior angulation of left pulmonary artery.

clot in spite of being passed for long distances down the artery on both sides. Neuhof stated, "A metal tube with an appropriately hollowed end would probably be more effective in engaging and extracting the thrombus."[1] We, in fact, did use a curved metal suction tip, but because of its small bore and the angulation of the vessel, were unable to bring it into effective apposition to the more distal portions of the thrombus. A glance at the pulmonary artery angiograms illustrated in Figures 2 and 4 will serve to illustrate the angulation of the pulmonary arteries. We have attempted to surmount this difficulty by construction of metal suction tips of graded diameters and lengths based on measurements of the pulmonary arteries as they progress toward the periphery of the lung. These suction cannulae are angled in the same fashion as the lumen of the artery and are malleable so that they may be altered on the operating table. (Figure3). The tube of larger diameter is designed for the vessel down to the point at which the upper lobe branch is given off. The tube of smaller diameter and greater length is for the vessel distal to that point. In addition we have made loops for stripping the thrombus from the vessel wall (Figure 5) and angled forceps for extracting the thrombus.

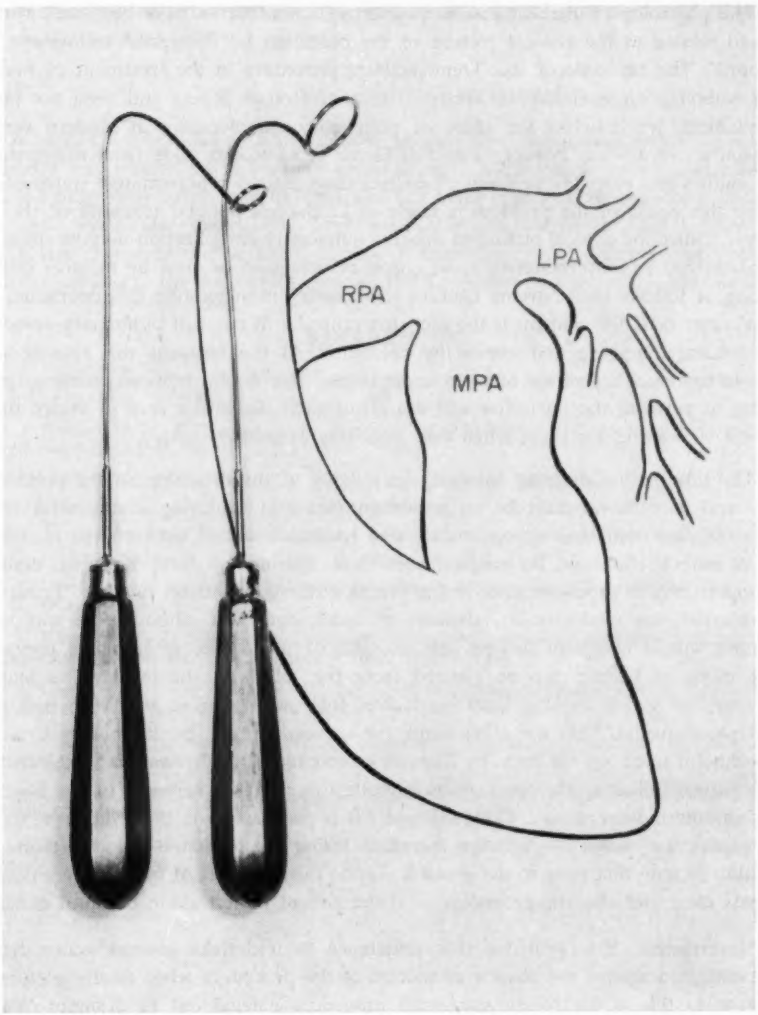

Figure 5

Thrombectomy loops photographed against 1:1 outline drawing of posterioranterior pulmonary angiogram. These have malleable shafts.

Following a successful embolectomy it would no doubt be advisable to interrupt the venous pathways from the lower extremities. In the case recounted here we had planned to proceed with bilateral femoral ligation. An inferior vena caval ligation might be preferrable in certain situations, but we thought that the postoperative abdominal situation in this case made this undesirable.

The physiological mechanisms in pulmonary embolization have been well worked out and related to the clinical picture of the condition by Churchill[6] and Giertz and Crafoord[7]. The rationale of the Trendelenburg procedure in the treatment of massive acute embolization is clearly set forth in these and other papers and need not be reviewed here. Nevertheless the place of pulmonary embolectomy in modern surgery has been a stormy one. Possibly a critical factor in its eclipse aside from the operative technicalities has been the problem of correct diagnosis. A representative statement regarding this phase of the problem is made in Lindskog's popular textbook of thoracic surgery: "Since the clinical picture of massive pulmonary embolization may be simulated by sudden heart failure resulting from coronary occlusion or even by massive internal bleeding, it follows that extreme caution is necessary in suggesting this operation . . . A final unpredictablie element is the fact that critically ill cases of pulmonary embolism may suddenly improve and eventually recover."[8] At the moment the attitude cited seems to represent a position of relative negativism. No doubt, however, most surgeons electing to perform the operation will use all of their diagnostic care to assure that a clot will be waiting for them when they open the pulmonary artery.

The time period elapsing between the lodging of the thrombus in the pulmonary artery and its removal must be an important factor in achieving a successful result. In the case reported here approximately two hours intervened between the manifestations of embolization and the surgical procedure. During this time the initial embolus had opportunity to propigate distally and create a situation difficult to undo. Trendelenburg himself was evidently an advocate of quick operation, although he was never rewarded with a complete success. An example of the degree of initiative prevailing in his clinic at Leipzig can be gleaned from the following statement, "Die Stationschwester, die gleich an eine Embolie dachte, fuhr den Kranken sofort im Bett nach dem Operationssaal."[5] On the other hand, the successful cases carried out by Crafoord in Stockholm were not achieved by haste in intervention, but by waiting at the bedside of the patient following the onset of the embolization until the certainty of the diagnosis made anesthesia unnecessary. Crafoord said, "It is permissable in doubtful cases, as our new experience shows — without therefore losing the patient — to postpone the operation so long that even to the greatest skeptic the diagnosis of obstructive embolism becomes clear and also the prognosis — if the patient be left alone becomes certain."[7]

Nevertheless, it is probable that reluctance to undertake prompt action has at times mitigated against the chance of success of the procedure when finally performed. Pertinent to this is the recent successful procedure carried out by Richard Warren in Boston (the first successful pulmonary embolectomy in this hemisphere) which was called to our attention following our own operation. His paitent, a 64 year old woman who sustained a massive embolization at 3:30 in the afternoon following cholecystectomy and choledochostomy, was operated on 45 minutes from the time of onset of the initial symptoms. In regard to the time factor Warren states, "The case has taught us, however, that although we should be wary of operating on a patient in whom the diagnosis may be incorrect, we must consider that we have reached a stage of progress where, once the diagnosis has been confidently made, we should be permitted to perform the operation without waiting until we are sure that the patient will not survive without it. The attitude, as described by Churchill, which in the past prompted one operating

team to remain alerted for 17 hours following embolism, to operate only as the patient died, should be a thing of the past."[8]

SUMMARY AND CONCLUSIONS

A patient who developed acute massive pulmonary embolization following subtotal colectomy was treated by pulmonary embolectomy. Although thrombus was removed from the pulmonary artery and its right and left main branches, the patient succumbed with right ventricular obstruction from residual thrombus in the distal pulmonary arterial tree. Some of the pertinent factors pertaining to this procedure are discussed and modifications in the instuments used for the Trendelenburg procedure are suggested.

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THE INJECTION OF NOXIOUS MATERIALS INTO THE HAND

ALEX P. KELLY, JR., M.D.*

In our present highly industrialized society, workers are exposed to many obvious hazards. They are protected by systematic study of these dangers by safety engineers, who develop methods and devices to decrease the hazards. No employer would allow a tyro to step up to a punch press and begin work without thorough orientation as to the dangers inherent therein.

The problem however, is to anticipate the hazards of innocuous appearing mechanical devices and protect against injury from them. Many novices handle high pressure grease guns without preliminary instruction, or trepidation. This device is capable of destroying a hand as thoroughly as any punch press.

The injury potential of the grease gun is shared by a number of devices which extrude a variety of liquids and semisolids through fine apertures in their nozzles. The propelling force may reach several thousand pounds per square inch due to the extremely small opening. At close range such a jet can penetrate skin and soft tissue. Pressure lubricating devices, fuel injection nozzles in gasoline and diesel engines, pressure guns for sealants, and plastic injection presses are some of the more familiar devices that can cause injection injury.

Figure 1 (a) and (b)

Grease gun injury of index finger showing diffuse damage and multiple draining sinuses.

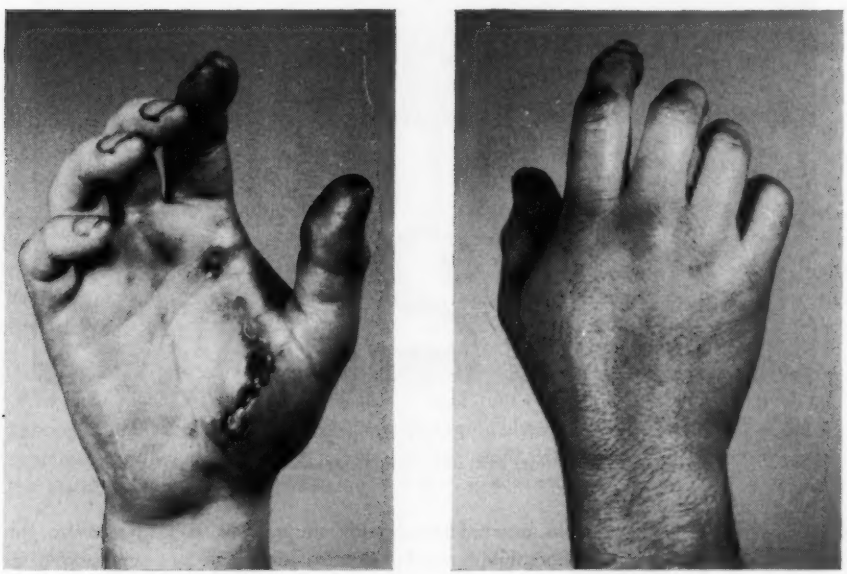
*Division of Plastic Surgery.

Stoppage of normal function may result in the operator exploring the nozzle with his finger or inserting a small wire into the aperture in an attempt to clear the malfunction. This places the hand in a position where injury is inevitable if the nozzle clears.

A number of cases of injection injuries of the hand have been encountered by the Plastic and Reconstructive Surgery Division. Three representative cases follow:

CASE 1. A 33 year old mechanic ran his finger over the nozzle of high pressure lubrication gun. He felt immediate discomfort. He was seen in the medical section of his plant where he was placed on warm soaks and antibiotics. He was seen in this hospital 9 days post injury with a marked swelling of the index finger and distal palm over the 2nd metacarpal area. The tissue was evenly indurated. He had no evidence of circulatory embarassment of the digit or of involvement of the spaces of the hand or wrist. He was continued on antibiotics and returned on the 21st post injury day with several localized flucuant areas over the proximal phalanx. These areas were drained as was a collection in distal palm. Saponified grease and necrotic tissue was removed from each of these areas. There was minimal improvement. Multiple small sinuses developed extruding white cheesy material. Amputation of the digit was advised but refused by the patient. The patient was able to work but the constant low grade discomfort and drainage made the patient consent to amputation, four months after injury. An index ray amputation was carried out which made it feasible to also clear the palm of all damaged tissue.

Figure 2
Sealing Compound Injury



(a) Swelling of thenar space

(b) Swelling of adductor space

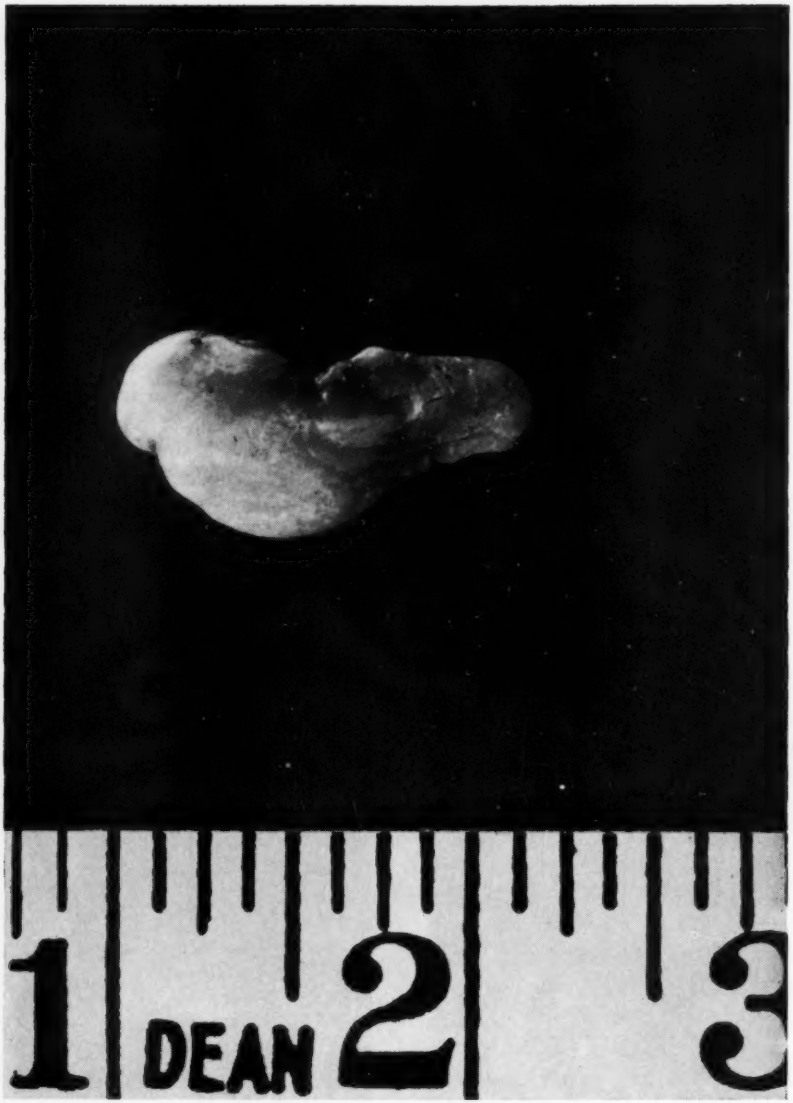


Figure 3

Plastic removed from wrist of Case 3. Longitudinal groove is the impression of the flexor carpi radialis.

CASE 2. A 42 year old male automobile assembly worker was using a pressure gun to seal crevices in an automobile body. He accidentally scraped the gun across his palm. He went to the medical section where it was assumed that the injury was

a superficial laceration contaminated with the sealing compound, the wound was cleaned and he was placed on antibiotics. In the next 12 hours pain and swelling increased. He was seen in this hospital 18 hours after injury where it was presumed he had cellulitis of the thenar area. No flucuation was noted. The hand improved on warm soaks and antibiotics. After 72 hours no further improvement was noted. Operative exploration was carried out. The thenar space was opened through the original wound. The space was filled with about 15 cubic centimeters of sealing compound. The adductor space was opened dorsally and approximately 5 cubic centimeters of sealant welled out. Drains were placed and in the ensuing few days the hand improved dramatically. After a few weeks the hand was asymptomatic except for dense scarring of the thenar musculature. A secondary procedure was carried out. The scar and small locule of sealing compound was removed. Virtually normal function was obtained post operatively.

CASE 3. A 40 year old female seen because of a stenosing tenosynovitis of her third finger. She had a scar in her palm as a result of a minor injury incurred 7 years previously on a plastic moulding machine. No treatment had been given at the time of injury and no symptoms had been noted other than the mass. At the time operation for the presenting complaint the palm was opened and a small mass of clear plastic was extracted. Eight months later the patient returned complaining of swelling of the wrist. This was felt to be a ganglion or adventitious bursa. At operation this was found to be a bursa overlying a plastic mass between the flexor carpi radialis and flexor sublimis tendons. The mass was moulded about the radialis tendon. Tissue reaction about the mass was negligible except for the aforementioned bursa. The post operative course was unevenful, after removal.

DISCUSSION:

The salient features of several types of injection injury have been illustrated. The minimal initial symptoms belie the gravity of the injury. An apparently minor injury with a pressure actuated injection device should be considered severe until proven otherwise. The tissue injury ensuing may be due to several factors. The quantity injected may be sufficient to cause interference with circulation. This is especially true in anatomically well compartmented structures such as the hand. The temperature of the injected material may cause thermal injury. The material may be a tissue irritant causing immediate acute inflammation or a more chronic response, such as granuloma formation. All of these factors may be present in a single injury.

Examination should include roentgenograms which may aid in localizing collections of injected material.[1] A careful physical examination of the hand should be conducted bearing in mind the injected material may be evenly dispersed in the soft tissue (Case 1), penetrate the digital theca and follow into the ulnar or radial bursa (Case 3), or fill the anatomical spaces (Case 2).

Management of the injury should be the immediate removal of the injected material if feasible. In the thermolabile plastic injury the material is solidified in a few moments. Removal must be through adequately and properly placed incisions. The

concomitant thermal injury makes it unwise to close the wound primarily.[2] The wound should be left open until all nonviable tissue has separated. Closure is then obtained secondarily by skin grafts or suture.

The injection of hydrocarbon fuels or lubricants presents a problem of immediate physical damage and continuing reaction due to granuloma formation. The reaction varys considerably because of varied composition of such products. Asphaltic or plastic sealants will also vary in the amount of tissue reaction elicited. The exact composition of the material should be sought and its toxicity determined. In early cases all indentifiable collections should be drained. This can result in dramatic improvement in the circulatory status and motion. After early measures have been exhausted, conservatism is indicated. The conservative course should be followed in all cases seen late.[3] Infection should be prevented. Drainage of necrotic areas as they appear and maintenance of proper joint posture should allow maximum salvage of function. The morbidity may extend over many months. When the damage is isolated to a single digit or segment of the hand judicious amputation can result in rapid restoration of usefulness to the hand. Amputation should be a last resort but should not be deferred until the patient is exhausted physically, emotionally and economically.

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INTERNATIONAL SYMPOSIUM ON OTOSCLEROSIS

November 10, 11, 12, 1960

The professional staff of the Henry Ford Hospital with the initial advice and support of the Board of Trustees and Dr. Robin C. Buerki, Executive Director, of the Henry Ford Hospital, sponsored an International Symposium on the subject Otosclerosis. This symposium was held at the Henry Ford Hospital, November 10, 11, and 12, 1960 in the Clinic Auditorium.

PROGRAM COMMITTEE

HAROLD F. SCHUKNECHT, M.D., *Chairman*

Director, Otological Research Laboratory, Associate Surgeon, Department of Otolaryngology, Henry Ford Hospital.

FRANZ ALTMANN, M.D.
Clinical Professor of Otolaryngology, Columbia University, College of Physicians and Surgeons.

J. LEWIS DILL, M.D.
Chief, Department of Otolaryngology, Henry Ford Hospital.

WILLIAM F. HOUSE, M.D.
Instructor in Surgery, University of Southern California Medical School.

MERLE LAWRENCE, Ph.D.
Professor of Otolaryngology and Physiology, University of Michigan Medical School.

JOHN R. LINDSAY, M.D.
Professor of Otolaryngology, University of Chicago Medical School.

JOHN J. SHEA, Jr., M.D.
Memphis Otologic Clinic.

NOVEMBER 10 —

FIRST SESSION: Anatomical, Pathological and Genetic Features of Otosclerosis.

Chairman: *Merle Lawrence,* Ph.D.

Professor of Otolaryngology and Phsiology
University of Michigan Medical School
Ann Arbor, Michigan

Otosclerosis

9:00 The Normal Histology of the Labyrinthine Capsule and the Oval Window Area.

Hans Engstrom, M.D., Associate Professor of Otology, Department of Otolaryngology, University of Göteborg, Göteborg, Sweden

9:20 Histopathology and Etiology of Otosclerosis.

Franz Altmann, M.D., Clinical Professor of Otolaryngology, Columbia University, New York City, New York

9:40 Studies of Otosclerotic Bone.

Harold M. Frost, M.D., Associate Surgeon, Department of Orthopaedic Surgery, Henry Ford Hospital, Detroit, Michigan

10:00 Comments on Sensorineural Hearing Loss in Otosclerosis.

Aram Glorig, M.D., Director of Research, Subcommittee on Noise Research Center, Los Angeles, California

10:20 Histopathology of Sensorineural Degeneration and other Inner Ear Changes in Otosclerosis.

Luzius Rüedi, M.D., Professor of Otorhinolaryngology, Director of the ENT Clinic, University of Zürich, Zürich, Switzerland

10:40 Intermission.

11:00 Neuroanatomical Correlates of Auditory Discrimination; Findings in Otosclerosis and Other Disorders.

Harold F. Schuknecht, M.D., Associate Surgeon, Dept. of Otolaryngology, Henry Ford Hospital, Detroit, Michigan.

11:20 Genetic Problems in Otosclerosis.

Anders Larsson, M.D., Dept. of Otolaryngology, University of Göteborg, Göteborg, Sweden

11:40 Designated Discussion.

Juergen Tonndorf, M.D., Associate Professor, Dept. of Otolaryngology, University of Iowa Medical School, Iowa City, Iowa

11:50 Designated Discussion.

Ben Senturia, M.D., Clinical Associate Professor, Dept. of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri

12:00 Open Discussion.

12:30 Lunch.

SECOND SESSION: Physiological Mechanisms Relating to Otosclerosis.

Chairman: *John R. Lindsay,* M.D., F.A.C.S.

Professor and Chairman, Dept. of Otolaryngology
University of Chicago Medical School and Associated Hospitals
Chicago, Illinois

2:00 The Transmission of Sound in the Ear.

Ernest Glen Wever, Ph.D., Professor, Princeton University, Princeton, New Jersey

2:30 The Physiological Significance of the Middle Ear Muscles.

Henry B. Perlman, M.D., Professor of Otolaryngology, University of Chicago School of Medicine and Associated Hospitals, Chicago, Illinois

2:50 Designated Discussion.

Merle Lawrence, Ph.D., Professor of Otolaryngology and Physiology, University of Michigan Medical School, Ann Arbor, Michigan

3:00 Open Discussion.

3:15 Intermission.

3:30 The Value of the Weber Test in Otosclerosis.

J. J. Groen, M.Sc., Lecturer in Labyrinthology, Ear, Nose and Throat Dept., State-University Utrecht, Utrecht, The Netherlands

3:50 Designated Discussion: Comments on Effect of Stapes Fixation on Bone Conduction Response.

Raymond Carhart, Ph.D., Professor, Audiology and Otolaryngology, Northwestern University, Evanston, Illinois.

4:00 Masking in Testing for Otosclerosis.

William G. Hardy, Ph.D., Associate Professor, Otolaryngology and Environmental Medicine, Johns Hopkins Medical Institutions, Balitmore, Maryland

4:20 Some New Objective Tests for Stapes Ankylosis.

Lennart Holmgren, M.D., Associate Professor, Karolinska Hospital, Stockholm, Sweden.

4:40 Open Discussion.

5:00 Adjournment.

NOVEMBER 11 —

THIRD SESSION: Fenestration of the Horizontal Canal.

Chairman: *Senator Joseph A. Sullivan,* M.D., F.R.C.S. (C)
Toronto, Canada

9:00 The Results, Techniques and Present Status of Fenestration Surgery.

Henry L. Williams, M.D., M.S., Professor of Otolaryngology and Rhinology, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minn.

9:20 The Place for the Fenestration Operation in the Surgery of Otosclerosis.

Ion Simson Hall, M.B., ChB., F.R.C.P.E., F.R.C.S.E., Surgeon in Charge, Ear, Nose and Throat Department, Royal Infirmary of Edinburgh, Edinburgh, Scotland

9:40 Fenestration: Results, Indication, Limitations.

Theo. E. Walsh, MRCS-LRCP, Professor of Otolaryngology, Washington University School of Medicine, St. Louis, Missouri

10:00 Open Discussion.

10:15 Intermission

10:30 A Study of Long Term Results of Fenestration Surgery.

Howard P. House, M.D., Clinical Professor of Otolaryngology, University of Southern California School of Medicine, Los Angeles, California

10:40 Histopathology of Fenestration, Animal and Human Studies.

Dorothy Wolff, Ph.D., Associate Professor of Otorhinolaryngology, New York State University, Downstate Medical Center, Brooklyn, New York

11:00 Cochlear Pathology Following Fenestration and Stapes Surgery.

George E. Shambaugh, M.D., Professor and Chairman, Dept. of Otolaryngology, Northwestern University Medical School, Evanston, Illinois

11:15 Designated Discussion.

J. H. Thomas Rambo, M.D., New York City.

11:30 Open Discussion.

12:00 Movie Film honoring the late *Heinz Kobrak,* M.D., Ph.D.*

Formerly, Associate Professor, Dept. of Otolaryngology, University of Chicago School of Medicine, Chicago, Illinois

*Formerly, Professor of Otology, Dept. of Industrial Medicine, Wayne State University, Detroit, Michigan

12:30 Lunch.

FOURTH SESSION: Research Relating to Stapes Surgery.

Chairman: *Edmund P. Fowler, Jr.,* M.D.

Professor and Chairman, Dept. of Otolaryngology
Columbia University School of Medicine
New York City, New York

2:00 Acoustic Trauma from Surgical Instruments.

Michael M. Paparella, M.D., Dept. of Otolaryngology, Henry Ford Hospital, Detroit, Michigan

2:20 The Effects of Hemorrhage into the Vestibule (Animal Experiment).

Albert Hohmann, M.D., Clinical Instructor, University of Minnesota, Minneapolis, Minnesota

2:40 Experimental Studies on the Stapes.

John J. Shea, Jr., M.D., Memphis, Otologic Clinic, Memphis, Tennessee

3:00 Repair and Consequences of Surgical Trauma to the Ossicles and Oval Window of Experimental Animals.

Richard J. Bellucci, M.S., M.D., Surgeon-Director, Manhattan Eye, Ear and Throat Hospital, New York City, New York

3:20 Intermission.

3:40 Bone and Soft Tissue Repair Following Stapes Surgery (Animal Experiments).

Harold F. Schuknecht, M.D., Associate Surgeon, Dept. of Otolaryngology, Henry Ford Hospital, Detroit, Michigan

4:00 Histopathology of Stapes Surgery in Autopsy Specimens.

Franz Altmann, M.D., Clinical Professor of Otolaryngology, Columbia University College of Physicians and Surgeons, New York City, New York

and *John R. Lindsay,* M.D., F.A.C.S., Professor and Chairman of Otolaryngology, University of Chicago Medical School and Associated Hospitals, Chicago,, Illinois

4:20 Experiences and Studies in Advanced Otosclerosis.

William F. House, M.D., Instructor in Surgery, University of Southern California, Los Angeles, California

4:40 Open Discussion.

5:00 Adjournment.

NOVEMBER 12 —

FIFTH SESSION: Stapes Surgery.

Chairman: *Terence Cawthorne,* M.D., F.R.C.S.

London, England

9:00 Introductory Remarks.

Philip E. Meltzer, M.D., Professor and Chairman, Dept. of Otolaryngology, Harvard University School of Medicine, Boston, Massachusetts

9:15 Is There a Single Stapes Operation Preferable for all Cases of Otosclerosis?

Samuel Rosen, M.D., Consulting Otologist, New York Eye and Ear Infirmary, Mt. Sinai Hospital, New York City, New York

9:30 Fenestration of the Oval Window After More Than Four Years.

John J.Shea, Jr·, M.D., Memphis Otologic Clinic, Memphis, Tennessee

9:45 "Interposition" Procedure for Stapes Ankylosis.

Michel Portmann, M.D., Professur Agrege ORL, University of Bordeaux, Bordeaux, France

10:00 Experiences with Stapes Surgery.

Howard P. House, M.D., Clinical Professor of Otolaryngology, University of Southern California School of Medicine, Los Angeles, California

10:15 Audiosurgery of Otosclerosis. Relationship Between the Histology, Microscopic View, and Surgical Technique.

Francisco Antoli-Candela, M.D., Chief of Audiology Service of the National Institute of Medicine, Madrid, Spain

10:30 Discussion.

10:45 Intermission.

11:00 The Anterior Position, Articulated Prosthesis, and Audiometric Guidance in Stapes Surgery.

Victor Goodhill, M.D., Clinical Professor of Surgery (Otology), University of Southern California School of Medicine, Los Angeles, California

11:15 Technique and Experiences with Stapedectomy and Metal Implant.

T. Manford McGee, M.D., Associate Surgeon, Dept. of Otolaryngology, Henry Ford Hospital, Detroit, Michigan

11:30 Vein Plug Stapedioplasty.

Claire M. Kos, M.D., Director, Iowa Clinic of Otology, Iowa City, Iowa

11:45 Circumscribed Stapes Surgery in Circumscribed Otosclerosis.

J. Brown Farrior, M.D., Otologist, Farrior Clinic, Tampa, Florida

12:00 Experiences in the Surgical Management of Otosclerosis.

Fred R. Guilford, M.D., Associate Professor of Otolaryngology, Baylor University School of Medicine, Houston, Texas

12:15 Discussion.

12:30 Lunch.

SIXTH SESSION: Stapes Surgery and Summarizations.

Chairman: *Ion Simson Hall,* M.B., ChB., F.R.C.P.E., F.R.C.S.E.

Surgeon in Charge, ENT Department
Royal Infirmary of Edinburgh
Edinburgh, Scotland

2:00 Experiences with Enlarging the Oval Window After Removing the Footplate.

Hans Heermann, M.D., Chefarzt der HNO-Abtlg., Krupp-Krankenanstalten, Mitglied der "Deutschen Gesellschaft fur Hals-, Nasen-, Ohren", Essen Germany

2:15 Total Stapedectomy in the Surgical Treatment of Otosclerosis.

David Myers, M.D., F.A.C.S., F.I.C.S., Professor and Head of the Dept. of Otohinology, Temple University School of Medicine, Philadelphia, Penn.

2:30 Further Evolution of Otosclerosis Surgery: Graduated By-Pass Stapes Operations.

Eugene L. Derlacki, M.D., Associate Professor of Otolaryngology, Northwestern University Medical School, Chicago, Illinois

2:45 Stapedectomy, Reconstruction with Vein Graft and Bone Strut.

F. Zöllner, M.D., Professor and Director, Dept. of Otolaryngology, University of Freiburg, Freiburg, Germany

3:00 Long Term Results in the Fenestration Operation, Comparative Short Term Results in Stapes Mobilization, and Interpositioning Operation.

Luzius Ruedi, M.D., Professor of Otorhinolaryngology, Director of ENT Clinic. University of Zürich, Zürich, Switzerland

3:15 General Discussion.

3:30 Intermission.

3:45 Summarization of the Symposium.

John R. Lindsay, M.D., F.A.C.S., Professor and Chairman of Otolaryngology, University of Chicago Medical School and Associated Hospitals, Chicago, Illinois.

4:15 Otosclerosis and Clinical Research.

Gordon D. Hoople, M.D., State University, Upstate Medical Center, Syracuse, New York

4:30 Adjournment of the Symposium.

SPECIAL AWARDS

Dr. William S. Haubrich is the recipient of the Vincent Lyon award of the American Gastroenterological Association in recognition for the best presentation by an associate member of the society at its annual meeting. Dr. Haubrich presented a study of the anatomic changes of Whipple's disease demonstrated by light and electron microscopy.

Dr. Harold F. Schuknecht has the distinguished honor of having been named the recipient of the Achievement Award and $1000 for outstanding research on deafness from the Deafness Research Foundation.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

***REGULATION OF CHOLESTEROL MOBILIZATION IN MICE BY BILE ACIDS.** W. T. BEHER, W. L. ANTHONY AND G. D. BAKER. Proc. Soc. Exper. Biol. & Med. 103:531, 1960.

The effects of cholic and hyodeoxycholic acids on mouse liver and carcass cholesterol mobilization were investigated. Cholic acid inhibited liver cholesterol mobilization, while hyodeoxycholic acid promoted a rapid elimination of accumulated liver cholesterol. Hyodeoxycholic acid reversed the inhibition caused by cholic acid. Neither of these substances effected the rate of carcass cholesterol mobilization.

THE PLACE OF TOTAL THYROIDECTOMY IN SURGERY FOR THYROID CARCINOMA. M. A. BLOCK, R. C. HORN AND B. E. BRUSH. A.M.A. Arch. Surg. 81:236, 1960.

In our experience, the over-all frequency of multicentricity in carcinoma of the thyroid is at least 13%. In a group of total or near total thyroidectomies, the figure was found to be at least 23%. These figures probably represent the minimal expression of the true incidence of this feature. The occurrence of multicentricity appears to justify total or near total thyroidectomy for most patients undergoing surgery to cure thyroid carcinoma. Evidence suggests this is especially true for patients under age 21 years. An anatomic dissection is required in performing total thyroidectomy to preserve parathyroid tissue on one side of the neck. If parathyroid tissue is not identified and preserved on the side of the neck opposite the primary or predominant lesion, it is usually preferable to leave a remnant of thyroid tissue in the region of the normal location of the parathyroid glands on this side of the neck. In a few patients, curative surgery requires sacrifice of all parathyroid tissue because of extensive bilateral carcinoma.

***EFFECT OF CORTICOTROPIN AND GROWTH HORMONE ON ALLANTOIN SYNTHESIS AND EXCRETION IN THE DOG.** H. C. CHOITZ AND O. H. GAEBLER. Proc. Soc. Exper. Biol. & Med. 104:475, 1960.

Growth hormone increased the amount of ammonium citrate-N^{15} utilized for allantoin synthesis in dogs. Corticotropin did not have this effect. Neither hormone increased incorporation of N^{15} from glycine into allantoin. Corticotropin increased the output of urinary allantoin in dogs, without markedly reducing the specific enrichment with N^{15} in this excretory product. One possible interpretation of this finding is increased synthesis of allantoin, without qualitative changes in its origin.

FAMILIAL RECURRING POLYSEROSITIS. W. R. EYLER, R. K. NIXON AND R. J. PRIEST. Am. J. Roentgenol. 84:262, 1960.

In a patient of Armenian, Syrian or Jewish background who presents with an attack of pain which could be caused by inflammation of one of the serosal surfaces

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and, in particular, if he gives a history of recurrent attacks, familial recurring polyserositis should be considered. The radiologist can be of some assistance in making this diagnosis. Roentgenologic findings in familial recurring polyserositis are for the most part nonspecific, but are helpful in confirming a diagnosis. During attacks of abdominal pain, plain roentgenograms of the abdomen show small intestinal ileus and a barium meal study shows discontinuity of the column, dilatation and delay in transit. During attacks of pleural pain, basilar atelectasis is generally demonstrated and pleural fluid in small to moderate amounts is often found.

ILEORECTAL ANASTOMOSIS IN ULCERATIVE COLITIS. L. S. FALLIS AND J. BARRON. A.M.A. Arch. Surg. 81:444, 1960.

The necessity for removal of the entire colon in the surgical treatment of ulcerative colitis has been well established, and there is sufficient documentary evidence to suggest that the indications for subtotal colectomy are very limited. Success with the figure-of-9 loop type of anastomosis in the conversion of a Billroth II to a Billroth I type of operation has led us to apply this principle to the anastomosis between the ileum and the rectum. Rectal continence is of course a definite requirement, and operation should not be considered in patients with impaired sphincteric control. The loop type of ileorectal anastomosis has now been carried out in 26 cases, of which 20 were for ulcerative colitis and 6 for multiple polyposis. We have been agreeably surprised by the relatively good results which this procedure has yielded. Our experience confirms the opinion of Aylett and Turnbull that the operation is feasible and can be performed without unduly jeopardizing the patient's life. A long-term follow-up study will be necessary to determine whether or not these patients will have serious exacerbations in the remaining rectum to the point that their health and well-being are menaced, and, of course, the question of development of carcinoma in the rectal stump is one that must receive serious consideration.

TUMORS OF THE MINOR SALIVARY GLANDS. G. FINE, R. B. MARSHALL AND R. C. HORN, JR. Cancer 13:653, 1960.

The clinical and morphological features of 79 benign and malignant epithelial tumors of minor salivary glands of the oral cavity have been reviewed and compared to previously reported tumors. Classification, frequency, and distribution of our 42 cases of 718 cases of benign tumor from the literature are given. Histologic type, frequency and distribution of our 37 cases and of 348 cases of malignant tumors from the literature are presented. Attention has been called to differences and similarities between these and the major salivary gland epithelial tumors and the need for recognizing and segregating a group of cellular tumors (adenomas) from the malignant group.

*ON THE NATURE OF THE FLUORESCENCE OF ENZYME — DPNH COMPLEXES. H. F. FISHER AND L. L. MCGREGOR. Biochem. Biophys. Acta. 38:562, 1960.

The discovery that the addition of a DPNH-linked enzyme to a solution of DPNH causes an increase in the intensity of fluorescence and a shift of the emission spectrum to shorter wavelengths, has provided an elegant and versatile tool for the

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investigation of enzyme-coenzyme complexes. However, the usefulness of such studies has been sharply limited by the lack of any generally valid and experimentally substantiated explanation of the phenomenon. Hypotheses involving changes in the structure, conformation, planarity, or electron distribution of the reduced nicotinamide ring have been widely proposed. We have found, however, that the binding of DPNH in *any* manner which reduces the possibility of inter- or intra-molecular collisions will cause both an increase in fluorescence intensity and a shift of the emission spectrum to shorter wavelengths.

*THE MECHANISM OF THE GLUTAMIC DEHYDROGENASE REACTION. I. THE MOLECULARITY OF THE FIRST COMPLEX FORMED. H. F. FISHER. J. Biol. Chem. 235:1830, 1960.

The increase in the fluorescence of DPNH caused by the addition of glutamic dehydrogenase and the further enhancement of that increase by the reduced substrate of that enzyme have been reported and interpreted as evidence of complex formation. Similar phenomena have been described for other coenzyme I linked dehydrogenases, but in no case has proof been obtained directly relating the observed phenomena to complexes actually shown by kinetic evidence to be directly in the reaction sequence. This paper presents evidence that the observed fluorescence increase is in fact a direct measure of the active enzyme-reduced coenzyme complex, and assigns to that complex a definite position in the kinetically determined reaction sequence. The results of related experiments which provide direct support for that kinetically determined reaction sequence are described. The first step in the glutamic dehydrogenase reaction is the formation of a complex between the reduced coenzyme and the "active" site of the enzyme. The increase in the fluorescence of TPNH caused by addition of enzyme is a direct measure of the formation of that complex. α-Ketoglutarate cannot combine with the enzyme itself, but only with the enzyme-reduced coenzyme complex.

*THE ROLE OF ELECTRON MICROSCOPY IN THE DEVELOPMENT OF A NEW SCIENCE "CRYSTALLURGY". M. W. FREEMAN AND J. H. L. WATSON. Fourth International Conference on Electron Microscopy, 1958. Berlin, Springer-Verlag, 1960, v. 1, p. 472.

The new understanding of the electronic structure of metals and of the role of lattice imperfections in determining their physical properties have been centered primarily in concepts of the single crystal, i. e. the concept of regular arrays of metallic atoms in relatively simple lattices, with any deviations from regularity restricted to certain limited varieties, which in particular do not include imperfections of the grain boundaries. This improved understanding which is increasing dramatically from year to year supplies the foundation of crystallurgy. "Crystallurgy" is defined as the science of the working of, or with crystals. In particular it is the study of methods to combine into gross forms. It begins with an understanding of the single crystal and then builds polycrystalline materials which have predictable properties. If properties can be predicted it follows that they can be made optimum.

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*MAGNETISM IN MEDICINE. M. W. FREEMAN, A. ARROTT AND J. H. L. WATSON. J. Appl. Physics 31:404S, 1960.

The applications of magnetic materials and magnetic fields in medicine are reviewed. Direct biological effects of magnetic fields, clinical uses of the mechanical force exerted by magnets, and magnetic analysis as a tool in biochemistry are considered. The authors' applications of the technology of fine particle iron to the treatment of cancer and mental disease for investigation of basic biochemistry and for diagnostic purposes are discussed. A significant step in these applications has been the discovery of sublingual assimilation of fine particle iron.

REPEATED ASSOCIATION OF STAPHYLOCOCCAL ANTIBIOGRAMS AND PHAGE TYPES. J. E. GREER AND R. R. MENARD. Bact. Proc. 1960, p. 102.

In an epidemiological study of antibiograms (ABG) and phage types (PT) of nasal and cutaneous strains of *Staphylococcus aureus* from 150 dermatological patients, no ABG was always associated with any particular PT, and *vice versa*. Nevertheless, any particular ABG-PT combination occurring, generally remained the same in subsequent repeat cultures from the same or related patients. Usually a change in ABG was accompanied by a change in PT, and *vice versa*. The change in PT without change in ABG occurred rarely, indicating that phage typing of repeat cultures, in surveys on the same patient, need be done only if the ABG changes. The constancy of the antibiograms from the same sources was a valuable and necessary adjunct in strain identification when variability in phage patterns made strain relationships uncertain.

PREMATURE SEPARATION OF THE NORMALLY IMPLANTED PLACENTA. C. P. HODGKINSON AND J. NEUFELD. Clin. Obst. & Gynec. 3:585, 1960.

The term "premature separation of the normally implanted placenta" describes the basic pathology of the most common and most serious cause of uterine bleeding in mid and late pregnancy. Its management is discussed under terminology, statistics and etiology. Clinical experience suggests that there are two types of placental abruption, one mainly arterial associated with toxemia, nephritis, and essential hypertension, one mainly venous produced by compression of the venous return from the uterus. The pathology and treatment are reviewed emphasizing the immediate necessity of determining the severity of the disease, the state of coagulability of the blood and how soon the patient is likely to deliver.

PRIMARY ADENOCARCINOMA OF THE FEMALE URETHRA: A REVIEW AND REPORT OF 3 CASES. R. KNOBLICH. Am. J. Obst. & Gynec. 80:353, 1960.

The glands surrounding the female urethra are homologous to the cranial and ventral lobes of the male prostate. In experimental animals the "female prostate" can develop into comparatively large structures by injection of androsterone and its derivatives. Adenocarcinomas of the female urethra arise from these paraurethral glands. Forty-one cases were collected from the literature and 3 new cases added. The adenocarcinoma of the female urethra is almost exclusively a disease of menopausal or

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postmenopausal women. There does not seem to be any racial predilection or relationship between multiparity and the occurrence of these adenocarcinomas. The majority of adenocarcinomas involve the distal urethra. The onset is usually insidious, symptoms including hematuria, dysuria, blood discharge, incontinence and local pain. Urethral obstruction with retention and uremia occurs in 15 per cent of the patients. Metastases from adenocarcinomas of the female urethra are not infrequent. Most of the adenocarcinomas of the female urethra drain into the more superficial lymphatics of the vulva and thereby to the nodes of the inguinal region. In untreated patients death occurs within a couple of months. The most efficient treatment for this type of tumor seems to be local resection and radium or roentgen therapy to the tumor and the involved inguinal nodes. Involvement of the entire urethra and inguinal nodes metastases are poor prognostic signs. The experimental demonstration that the paraurethral glands respond to androgenic hormones by hypertrophy as does the male prostate suggests the possibility of supplementing surgical and radiation therapy by administration of estrogens.

EFFECT OF PROLONGED GRISEOFULVIN ADMINISTRATION ON LIVER, HEMATOPOIETIC SYSTEM, AND KIDNEY. C. S. Livingood, M. Brannen, R. L. Orders, J. B. Kopstein and J. W. Rebuck. A.M.A. Arch. Dermat. 81:760, 1960.

Griseofulvin was given to 66 patients with superficial fungus infections; patients were carefully observed for side-effects and possible toxicity. In adults, the dosage schedule was 250 mg. q.i.d. and in children 125 mg. or 250 mg. b.i.d. or t.i.d. depending on the age and weight of the patient. The only side-effects seen in our study were four cases of headaches, one of abdominal cramps, and one of slight insomnia. All of these manifestations disappeared while the patients were still under therapy. Griseofulvin appears to be an effective, safe, and relatively nontoxic antibiotic for the treatment of various types of superficial fungus infections. If future findings confirm the earlier studies, griseofulvin will prove to be one of the significant advances in dermatology.

*THE APPLICATION OF X-RAY DIFFRACTION TO MEDICAL PROBLEMS. J. Parsons. *In* Mueller, W. M., ed.: Advances in X-ray Analysis; Proc. of the Eighth Annual Conference on the Applications of X-ray Analysis, 1959, New York, Plenum Press, 1960, v. 3, p. 349.

The use of the x-ray diffraction Debye-Scherrer powder technique for the identification of crystalline material often found in pathologic tissue is discussed. Cases cited include: heart calcification, lung silicosis, thorium dioxide in liver and spleen, and granulomas of the skin and pericardium. The routine analysis of kidney stones using powder cameras as well as an x-ray diffractometer are described.

SKIN WINDOWS AND THE ACTION OF THE RETICULOENDOTHELIAL SYSTEM IN MAN. J. W. Rebuck, C. B. Boyd, and J. M. Riddle. Ann. New York Acad. Sc. 88:30, 1960.

Aschoff, in his extension of Metchnikoff's general defense system of cells, included only those cells that were found to have an affinity for vital dyes. Since his methods were applied to the study of such a system of phagocytes in laboratory animals,

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we modified his method for study of those cells phagocytic for the same vital dyes (pyrrol blue, lithium carmine, trypan blue, and trypan red) in skin windows in man. In such inflammatory lesions lymphocytes, hypertrophied lymphocytes, macrophages, and monocytes all showed an ability to store the above-listed vital dyes. Recently Marshall claimed demarcation in sterile inflammatory exudates in rabbits between lymphocytes that could not be impregnated with silver and metalophil system of their fellow histiocytes or macrophages and monocytes. Applying his techniques to the progressive influx of mononuclears in human skin windows, lymphocytes were strongly metalophilic at 9 and 12 hours of inflammation in man, and hypertrophied lymphocytes were similarly metalophilic at 14 hours of inflammation. The importance of the granulocytic interrelationships with proper RES functions in these lesions was emphasized by correlation of low neutrophilic participation with low lymphocytic responses and increased basophilic leukocytic migrations with impaired mononuclear defenses.

FILM: STAPEDECTOMY AND GRAFT-PROSTHESIS OPERATION. H. F. SCHUKNECHT. Acta oto-laryng. 51:241, 1960.

Because the stapes mobilization procedure so frequently fails as a result of reankylosis of the footplate after a period of months or years, there has been a trend towards stapes replacement surgery.

Since 1956 I have used tantalum and stainless steel wire for partial stapes replacement, but in these cases the footplate was left intact. After several months it became obvious that the footplate reankylosed in many of these operations and it was necessary to remove it completely. Because an experiment performed in our laboratory demonstrated that tantalum wire was well tolerated in the middle ear for a period of months, we continued to use tantalum (and sometimes stainless steel) and devised a complete stapes replacement operation. The tantalum or stainless steel wire (.005 inches) is knotted around a fat or connective tissue graft of appropriate size. The opposite end of the wire prosthesis is fashioned into a buttonhook shape. The entire prosthesis is about 4½ mm. long. This is introduced so that the soft tissue lies within the oval window and the buttonhook is firmly attached to the incus.

Although it is too early to evaluate the results, it is quite obvious that the incidence of excellent hearing maintained over a period of months is much greater than with any previous procedure used in our hands.

FUNCTIONAL ALTERATIONS FROM SENSORY-NEURAL LESIONS. H. F. SCHUKNECHT. In, Jackson, C., and Jackson, C. L., eds.: Diseases of the Nose, Throat, and Ear, ed. 2, Philadelphia, Saunders, 1959, pp. 383-395.

Loudness recruitment is characteristically present in Meniere's disease and stimulation deafness and other disorders which primarily involve the organ of Corti. Simply stated, it means that with increase in stimulus intensity there is an abnormally rapid rise in loudness sensation, so that even though there is a threshold loss, loudness sensation at high stimulus intensities will approximate or equal that of a normal ear. A reasonable explanation follows: The neurophysiologic correlate of loudness is thought to be the total number of impulses transmitted in the acoustic nerve fibers per unit period of time, the variables being the number of nerve fibers involved and the frequency

of the impulses in these nerve fibers. The two requirements for loudness recruitment, therefore, seem to be (1) a normal or near-normal nerve fiber population and (2) a damaged organ of Corti having a hair cell population which is diminished enough to account for a threshold loss but adequate enough to excite normal numbers of nerve fibers at high stimulus intensities. The manner by which residual inner hair cells in a pathologically affected ear activate large numbers of nerve fibers is not entirely clear. It is known that a great number of peripheral nerve fibers have their endings only on external hair cells. One explanation may be that the electric potentials developed by the remaining hair cells become sufficiently large and strong at the high stimulus intensities to activate nerve fibers which pass near the cells. It is known also that the ear manifesting loudness recruitment is better able to detect small changes in stimulus intensity, a phenomenon known as the "decreased intensity difference limen". This is logical enough for it seems obvious that unit changes in intensity occurring within the sensitivity range of such a diseased ear would affect more fibers and hence create greater changes in loudness sensation than in a normal ear. Therefore, loudness recruitment and decreased intensity difference limen appear to be manifestations of an incomplete sensory lesion with a normal or near-normal spiral ganglion.

On the other hand, with lesions involving the auditory neural pathways, e. g., acoustic neurinoma, and the neural atrophy type of presbycusis, the characteristic auditory manifestations are loss of ability to understand speech out of proportion to loss for pure tone thresholds. It appears that the auditory nerve fibers are important channels in a communication system. In recent years communication theory and concepts on information transmission have been expressed in precise, mathematical terms. Although few are interested in, or capable of understanding the mathematics involved, the fundamental concepts are simple. The ear analyzes speech by recoding the sound signals into nerve impulses which then travel along the auditory nerve. The fundamental coding method is very simple in that a nerve impulse is either present or absent. This principle of all or none is basic to neurophysiology. Another limitation is that a single nerve fiber can carry a maximum of only 800 to 1000 impulses per second. We can enumerate the variables in a neural pattern as follows: (1) the frequency of impulses in a single fiber, (2) the time relations between impulses in various fibers, (3) the selectivity as to which fibers are being activated, and (4) the number of fibers activated. In spite of the all-or-none law the normal auditory pathways can carry all the information required for intelligibility of the spoken voice. This is possible because of the tremendous number of channels in the communication system, because we know there are about 35,000 nerve fibers in the human auditory nerve. In the diseased ear with a loss of nerve fibers a limitation is imposed on the coding mechanism so that the amount of information which can be transmitted from the ear to the brain is less than normal. This deficiency in the number of nerve fibers results in an auditory system which can transmit simple signals (pure tones) of threshold magnitude, but cannot handle the complex signals of speech.

THE METAL PROSTHESIS FOR STAPES ANKYLOSIS. H. F. SCHUKNECHT AND S. OLEKSIUK. A.M.A. Arch. Otolaryngol. 71:287, 1960.

Early oval window surgery for the treatment of stapes ankylosis due to otosclerosis was of the indirect type in which attempts were made to mobilize the footplate by

forces transmitted through the crura. Very often these procedures resulted in crural fracture and, for this reason, a direct footplate approach soon was advocated by many otologists. These direct attempts consisted of the use of chisels, pneumatic hammers, and picks of various types. The direct attack on the footplate resulted in higher success rates because the number of crural fractures was reduced, but in many cases the hearing was lost again because of reankylosis of the footplate. It became evident, therefore, that there were two unsolved problems in oval window surgery; accomplishing adequate mobilization while creating or maintaining a "columnella effect", and avoiding reankylosis.

In an experiment on cats we have shown that footplate fractures heal by bony reunion when the fragments are closely approximated but a slight separation or gap is bridged by a membrane. We endeavor to make use of this particular healing process to prevent reankylosis for if part, or all, of the footplate could be displaced inward so as to be separated slightly from the otosclerosis lesion and/or the margins of the oval window, the gap would be bridged by a mucoendosteal membrane, creating thereby a permanently mobile segment of the footplate.

The surgical design which was developed as the result of the discovery of the mucoendosteal membrane consisted of the following steps: removal of the head, neck and crura of the stapes; mobilization of the thin normal, or nearly normal, portion of the footplate with fine chisels; replacement of the crura with a prosthesis of sufficient length to depress the mobilized portion of the footplate slightly from contact with the surrounding bone and/or annular ligament.

Between October, 1956 and January, 1959, 166 metal protheses were introduced, of which 30 were tantalum and 136 of stainless steel. The average time lapse from operation to final audiogram was three months. The 30 db. level or better for the three speech frequencies was asquired by 142 (86%) patients. Twenty-two showed no change, and two had losses of 6 db. or more. The bone-air gap was closed 50% or more in 68% of the patients. These results are considerably superior to those achieved by methods we used previously.

We are convinced that oval window surgery is superior to fenestration surgery because it permits utilization of the transformer mechanism of the middle ear and avoids the problems resulting from exteriorization of the mastoid cavity. More time is required to evaluate the long term prognosis of this operative technique.

EXPERIMENTAL AORTIC ATHEROSCLEROSIS IN RABBITS FOLLOWING THE INGESTION OF DIHYDROCHOLESTEROL. J. C. Sieracki, W. T. Beher*, and G. D. Baker*. Angiology 11:343, 1960.

Ingested dihydrocholesterol, a constant companion of cholesterol, is atherogenic in rabbits. The atherosclerosis is different from that seen in cholesterol fed rabbits. The histologic sequence of events in these lesions over a 51-week period is described in some detail. The lesions occurred in the absence of a gross hyperlipemia or signi-

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ficant hypercholesterolemia. Chemical analysis of the blood suggest that the serum cholesterol is partially replaced by dihydrocholesterol during the course of the experiment.

COLON SPHINCTERS SIMULATING ORGANIC DISEASE. A. W. TEMPLETON. Radiology 75:237, 1960.

A brief review of colonic sphincters is given with attention to their location and probable source of origin. Five cases are presented in which organic colon disease, in particular, carcinoma at a sphincter site, was suspected on the initial barium enema study. Subsequent examinations in 4 cases and surgery in 1 failed to demonstrate any abnormality. The segments of narrowing must, in each instance, have been due to persistent spasm in the region of a colonic sphincter.

*EFFECTS OF MAGNETIC FIELDS UPON ANISOTROPIC IRON CRYSTALS. J. H. L. WATSON, A. ARROTT, AND M. W. FREEMAN. J. Appl. Physics 29:306, 1958.

Problems inherent to magnetic alignment of alpha iron crystals are discussed and explained by electron microscopic observation of the behavior of the single domain crystals under the effect of magnetic fields. With these specimens, which possess a fraction of magnetically unfavorable dendrites, intrinsic coercive forces of over 1700 oersteds have been measured without alignment.

*AN ELECTRON MICROSCOPICAL STUDY: SOME EFFECTS OF MAGNETIC FIELD UPON SINGLE, ANISOTROPIC ALPHA IRON CRYSTALS AND THE RELATION BETWEEN THEIR FINE STRUCTURE AND MAGNETIC PROPERTIES. J. H. L. WATSON AND M. W. FREEMAN. Fourth International Conference on Electron Microscopy, 1958. Berlin, Springer-Verlag, 1960, v. 1, p. 467.

From theoretical considerations several behaviour patterns were predicted, (1) it would be difficult to align any particle completely if there were counter-acting torques, and therefore it might be expected that many particles, even when completely isolated and ideally shaped, would not be in complete alignment with the field; (2) in a strongly dendritic particle there might be more torque active upon a set of its secondaries than upon the central stem itself and it would be expected therefore that such particles would frequently lie transversely to the field direction; (3) local dipole effects might be observed to interfere with the field effect and it would be expected that some free particles would take unaligned positions; (4) the torques might be sufficient to bend primary or secondary branches of particles held rigidly in one or more places; (5) rod-like particles would be expected to align more readily than well developed dendrites, and best alignment in samples containing both types of crystals would be found among rod-like particles. All of these observations predicted by theory were seen in the micrographs. From the general behaviour reported, it is not surprising that while separated small agglomerates can be aligned, if they bunch together in large streams before alignment it is impossible for the applied fields, no matter how large, to cause further alignment. From these studies it is reported again that minimum of secondary development. In addition the medium in which they are placed

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should offer some ideal impedance to allow particle rotation but to reduce the streaming effect which for this medium to do just this, and to fulfill this impedance requirement. At the same time it allows determination of the magnetic properties on a block which can be sectioned later to give direct correlation between magnetic results and particle alignment.

*AN ELECTRON MICROSCOPICAL STUDY: THE STRUCTURE AND MORPHOLOGY OF ULTRAMICROSCOPIC DENDRITES OF ALPHA IRON. J. H. L. WATSON. Fourth International Conference on Electron Microscopy, 1958. Berlin, Springer-Verlag, 1960, v. 1, p. 464.

Three papers describe the role of electron microscopy in the determination of certain properties of ultramicroscopic crystals of alpha iron and in the assessment of their uses. The crystals are produced in a unique process of controlled electrolysis under conditions which favor the deposition of single particles in discrete locations rather than in continuous plated layers. All of the crystals to be described are inherently dendritic regardless of their specific morphology. In addition, we have reason to believe that they are monolithic and of the same nature as "whiskers", except for their greatly reduced dimensions. Although the dendrites were examined extensively by the more usual electron microscopical methods, it was not until carbon replication with partial etching was applied to them, coupled with stereoscopy, that a structure was determined which was consistent with certain chemical kinetics of the reaction, as well as with the crystal structure itself of this body-centered, cubic material.

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